

Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

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## Preface

Volume 71 of *Advances in Heterocyclic Chemistry* consists of five chapters. In the first, Drs. D. Lloyd and H. McNab (St. Andrews and Edinburgh, Scotland) give an up-to-date treatment of 1,5-benzodiazepines. This subject was previously reviewed in 1974, but since then much new information has become available and a totally new approach was required. The second chapter by Professor El Ashry and Dr. N. Rashed of Alexandria University, Egypt, covers 1,2,3-triazolopyrimidines, including the three different types of [1,5-*a*]-fused, [1,5-*c*]-fused, and [4,5-*d*]-fused compounds. All these bicycles have recently seen much activity, particularly in the search for therapeutic agents.

Professor A. Haas (Bochum, Germany) deals with some of the recent developments in chalcogen-heterocycles with particular emphasis on simple sulfur, selenium, and tellurium compounds that can serve as synthons for the preparations of various heterocycles.

The next chapter represents the third in a series of articles by Dr. I. Hermecz on the chemistry of pyrido-oxazines, -thiazines, and -diazines. Part I, in Volume 69 dealt with pyridine ring [1,2-*b*]-fused to 1,2-heterocycles. Part II, in Volume 70 covered the [1,2-*c*]-1,3-fused derivatives, and the present Part III deals with pyrido[1,2-*c*]-1,4-oxazines, -1,4-thiazines, and -pyrazines. A final chapter on the [2,1-*b*]-1,3-fused compounds will appear in Volume 72.

The final chapter is part V of our ongoing series of surveys of the review literature of heterocyclic chemistry. It is authored by Professor L. I. Belen'kii and Dr. N. D. Kruchkovskaya (Moscow, Russia) and covers the years 1991 to 1993 inclusive.

ALAN R. KATRITZKY



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# 1,5-Benzodiazepines and 1,5-Benzodiazepinium Salts

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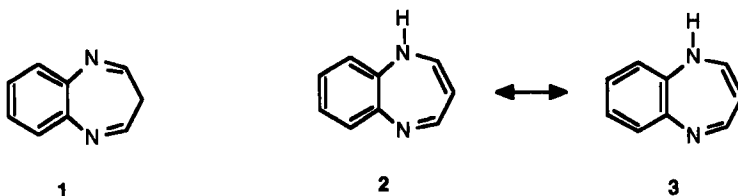
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I. Introduction . . . . .	2
II. Formation and Preparation of Benzodiazepines and Benzodiazepinium Salts . .	3
A. From 1,3-Dicarbonyl Compounds . . . . .	3
B. From $\beta$ -Chlorovinyl Carbonyl Compounds . . . . .	11
C. From $\alpha$ -Alkynyl Ketones . . . . .	12
D. Sundry Methods . . . . .	13
III. Structure . . . . .	18
IV. Spectra . . . . .	21
V. Basicity: Possible Use as Indicators . . . . .	23
VI. Reactions . . . . .	24
A. Hydrolysis: Ring-Contraction Reactions . . . . .	24
B. Oxidation . . . . .	27
C. Hydrogenation . . . . .	28
D. Reactions with Electrophiles . . . . .	29
E. Condensation Reactions . . . . .	33
F. Cycloaddition Reactions . . . . .	34
VII. 2(4)-Thio- and 2(4)-Aminobenzodiazepinium Salt . . . . .	36
A. Preparation of 2-Thiobenzodiazepines . . . . .	36
B. Reactions of 2-Thiobenzodiazepines . . . . .	37
C. Conversion of 2-Thiobenzodiazepines into 2-Aminobenzodiazepines . . . . .	38
D. Other Methods of Preparation of 2-Aminobenzodiazepines . . . . .	39
E. 2-Amino-3-cyanobenzodiazepines and 2-Amino-3-ethoxycarbonylbenzodiazepines . . . . .	41
VIII. 3-Oxo- and 3-Methylenebenzodiazepines . . . . .	46
IX. Metal Complexes . . . . .	48
References . . . . .	48

## I. Introduction

1,5-Benzodiazepines (**1**) are the 2,3-benzo-annelated derivatives of 1,4-diazepines. It should be noted that the numbering system for these benzodiazepines proceeds in the opposite direction from that used for the un-annelated diazepines. Therefore, the 1, 2, 3, 4, and 5 positions of the 1,5-benzodiazepines correspond respectively to positions 1, 7, 6, 5, and 4 in the monocyclic compounds. Throughout this chapter the term "benzodiazepines" refers exclusively to the 1,5-diazo isomers.

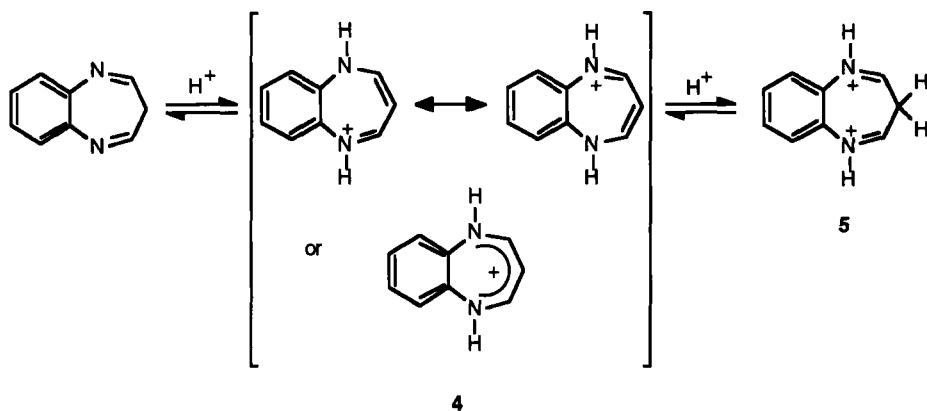


An earlier review on 1,5-benzodiazepines was published in *Advances in Heterocyclic Chemistry* in 1974 (74AHC27). The present article is not an addendum to or an updated version of that article but rather a completely new review. Much newer information is available, and different interpretations have been made about the chemistry of these compounds, so a totally fresh approach was required and has been adopted. There is an article on benzodiazepines in the Weissberger series of volumes on heterocycles, surveying literature up to 1984 (91HC209).

Benzodiazepines usually occur in the diimine form (**1**) rather than in the conjugated vinamidine forms depicted in formulas (**2**)  $\leftrightarrow$  (**3**). In the diimine form (**1**), some extra stabilization arises from the conjugation of the imine groups with the benzene ring. Cyclic conjugation as in (**2**)  $\leftrightarrow$  (**3**) may indeed lead to destabilization of the molecules because it involves interaction of 12  $\pi$ -electrons around the periphery of the molecule as implied in (**2**) or of 8  $\pi$ -electrons around the 7-membered ring as in (**3**); either of these are destabilizing  $4n$   $\pi$ -electron systems.

Protonation of benzodiazepines leads to the formation, successively, of monocations (**4**) and dications (**5**) (Scheme 1). The bases and dications are usually colorless or pale yellow, whereas the monocations are intensely colored, frequently dark purple.

1,5-Benzodiazepines have been rather overshadowed by the isomeric 1,4-benzodiazepines, which have been of enormous pharmacological interest, largely because of their very wide use as tranquilizers. Some 1,5-benzodiazepines also have physiological effects, *inter alia*, some 2-amino-4-phenyl derivatives as tranquilizers (80FES181) and some 2-*p*-fluorophenyl-



SCHEME 1

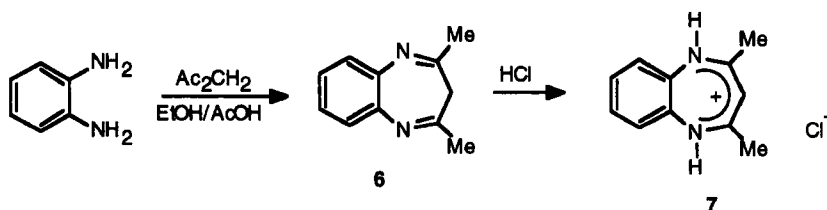
4-phenyl-8-chloro derivatives as antidepressants (in mice) (79MI1). Some 2-amino-4-methylthio derivatives act as depressants of the central nervous system and anticonvulsants, whereas 2,4-diamino analogs act as stimulants of the central nervous system and convulsants (79FES62). Certain benzodiazepines, in particular 2-thio derivatives, show antibacterial activity (75FES727, 75MI1; 77FES909), whereas some 2,4-dimethyl derivatives are said to have inhibited the growth of certain sarcomas in rats (74MI1).

Postemergence herbicidal activity has been shown by certain benzodiazepines (76MI1).

## II. Formation and Preparation of Benzodiazepines and Benzodiazepinium Salts

### A. FROM 1,3-DICARBONYL COMPOUNDS

The first example of a 1,5-benzodiazepine, the 2,4-dimethyl derivative (6), was prepared in 1907 by Thiele and Steimmig (07CB955), by condensation of *o*-phenylenediamine with acetylacetone in ethanol-acetic acid. Addition of hydrochloric acid precipitated the purple hydrochloride (7) (Scheme 2). The most common method of preparation of 1,5-benzodiazepines remains the reaction of *o*-phenylenediamine with 1,3-dicarbonyl compounds (84AF640). In addition to the 2,4-dimethyl derivative (33CB 1871; 40HCA1147; 59JCS1132; 60CB2752; 63JA3354; 65JCS3785; 85IC2276; 85IC2281) other 2,4-dialkyl derivatives have been made in this way (75MI2), including a 2,4-bis(bromomethyl) derivative (49HCA1584). A 2,4-bis(per-



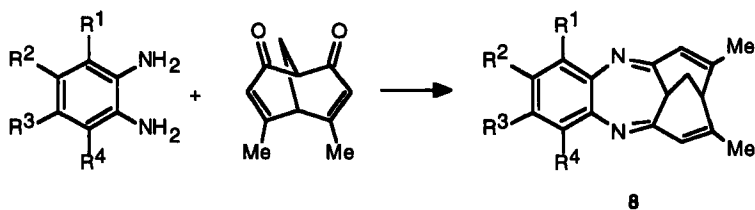
SCHEME 2

fluoroheptyl) compound has been prepared (74MI2), but attempts to prepare bis(perfluoromethyl) or bis(perfluoroethyl) analogs provided only benzimidazoles, although a 2-methyl-4-(pentafluoroethyl)benzodiazepine could be obtained (80IZV1172). Another report describes the 2,4-bis(trifluoromethyl) and 2-methyl-4-trifluoromethyl derivatives as unstable, decomposing in dilute aqueous acid or in air (72BCJ2942).

A rather more exotic 1,3-diketone has been converted into polycyclic benzodiazepines (**8**) by heating it with a variety of substituted *o*-phenylenediamines, usually in glacial acetic acid, but in some cases in ethanol containing mineral acid [78JCS(CC)557; 82JCR(M)0834, 82JCR(S)70] (Scheme 3).

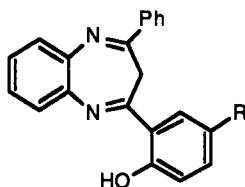
An alternative procedure starts from a metal complex of *o*-phenylenediamine. For example, the bis(*o*-phenylenediamine) complex of nickel(II) chloride reacts with acetylacetone to give a mixture of a nickel complex of the diamine and diketone together with 2,4-dimethylbenzodiazepinium chloride (76CPB1934; 91JPR327). Chromium complexes have been used in the same way [91JCS(D)2045].

As in the case of 2,3-dihydro-1,4-diazepines, formation of 2,4-diarylbenzodiazepines is less simple than that of their alkyl analogs, and more vigorous conditions are required. Thus 2,4-diphenylbenzodiazepine was made by heating dibenzoylmethane with *o*-phenylenediamine in boiling ethanol containing acetic acid (58JCS4094) or by heating the reagents in boiling xylene containing *p*-toluenesulfonic acid and removing water by azeotropic distillation (59JCS1132). Another variant involved heating the



SCHEME 3

diamine and diketone in the presence of molecular sieves in refluxing propanol (77AP964). Using either Thiele's original method or its modification by replacing ethanol by a higher-boiling solvent, a range of 2,4-diarylbenzodiazepines has been prepared (58JCS4094; 59JCS1132; 68PHA688; 70BCJ809; 75JIC849; 76JIC283; 79MI1; 84AF640; 88MI1). These diazepines also include 2-naphthyl-4-phenyl derivatives (75JIC849) and 2-heteroaryl(thienyl, pyridyl)-4-phenyl derivatives (76JIC283). The 2,4-diaryl compounds (**9**) are of interest in that they are fluorescent (85S339).



**9** R = Cl, Me

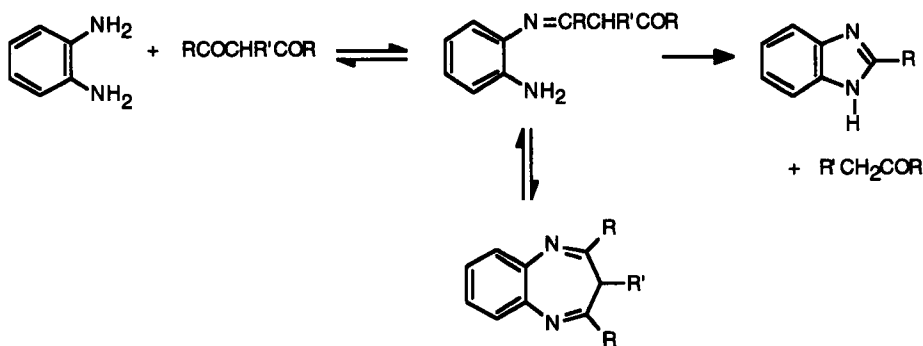
The phenolic group is not methylated by methyl iodide.

2-Methyl-4-arylbenzodiazepines can be made similarly from acylaroyl-methanes; 2-methyl-4-phenylbenzodiazepine was made in 1907 by Thiele (07CB955; 59JCS1132; 85IC2276, 85IC2281). Fluoroalkyl-4-phenyl (74MI2; 80IZV1172) and 2-methyl-4-heteroaryl (2'-selenienyl) (65JOU159, 65ZOR163), (2'-thienyl, 3'-pyridyl) (76JIC283), (quinoxalyl) (73AP401) and (coumarinyl) (74ZN580), have also been reported.

A variety of substituted *o*-phenylenediamines have been converted by similar methods into benzodiazepines [70CHE1061, 70KGS1135; 71CHE 519, 71KFZ218, 71KGS556; 73JHC891; 74RZC1073; 76JCSP(1)2353, 76MI2].

Bis(benzodiazepinyl) methanes have been made from bis-(3,4-diaminophenyl)methane and 1,3-diketones (74RZC1073).

2,3,4-Trimethyl-(38MI1; 40MI1; 40MI2; 63JA3354), 3-ethyl-2,4-methyl-(40MI1, 40MI2), and 3-(2'-benzimidazolyl)-2,4-dimethyl-(38JIC89) benzodiazepines have been prepared, but it appeared that when 2-substituted 1,3-diketones were reactants, the yields of benzodiazepine were lower, and this was explained as follows (63JA3354): It was suggested that formation of benzodiazepines involved the equilibria shown in Scheme 4. Some benzimidazole is usually formed as a by-product. It was assumed that if the equilibrium between the anil and the benzodiazepine lies very much on the side of the anil, then competitive formation of the benzimidazole dominates the processes. It was further suggested that if there were three vicinal substituents at the 2-, 3-, and 4-positions of the benzodiazepine, then steric hindrance between these substituents (well documented in the case of 2,3-dihydro-1,4-diazepines) would tend to destabilize the benzodiazepine and



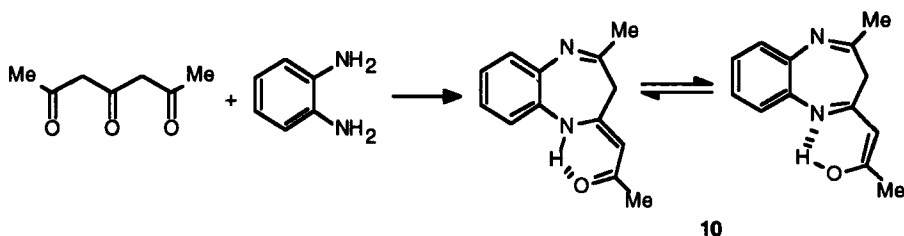
SCHEME 4

hence affect the equilibrium controlling its formation (63JA3354). However, these suggestions were made before NMR and crystallographic data indicated that the diazepine ring in benzodiazepines is boat-shaped (see Sections III and IV). Because the boat conformation can invert, the molecules will preferentially take up the conformation that minimizes vicinal crowding. More recent work [77JCS(P1)1901] has shown that 2,3,4-substituted benzodiazepines can be obtained in almost quantitative yield by carrying out the reaction in benzene containing a small amount of acetic acid, providing always that the size of the groups on the diketone does not impede access of the reactants to each other and that the groups are not strongly electron withdrawing. Despite this proviso, a crowded 2,3,4-substituted benzodiazepine [2,4-dimethyl-3-(*N*-methyl-3',4'-dihydrobenzoxazin-2'-on-4'-yl)benzodiazepine; see Section VIII] has been made in reasonable yield by heating the reactants together with a small amount of acetic acid and distilling off the water that is eliminated (80 JHC519), and 2,4-substituted benzodiazepine-3-phenylsulphonyl esters have been obtained by heating a mixture of *o*-phenylenediamine, acetylacetone, or benzoylacetone and an arylsulphonyl chloride (74MI3).

2,3-Cycloalkeno-4-methyl- or -4-phenyl-benzodiazepinium salts have been prepared from 2-acetyl- or 2-benzoyl-cycloalkanones (67JPR166).

No benzodiazepine has been obtained from *o*-phenylenediamine and 3,3-dimethylpentane-2,4-dione (38MI1; 40MI1, 40MI2; 63JA3354; 75TL91); a monoacylated 2,3-diaminophenazine formed by self-condensation of two molecules of the diamine and subsequent reaction with the diketone has been isolated from the reaction mixture. It is possible that diazepine formation requires the presence of some enol form of a diketone.

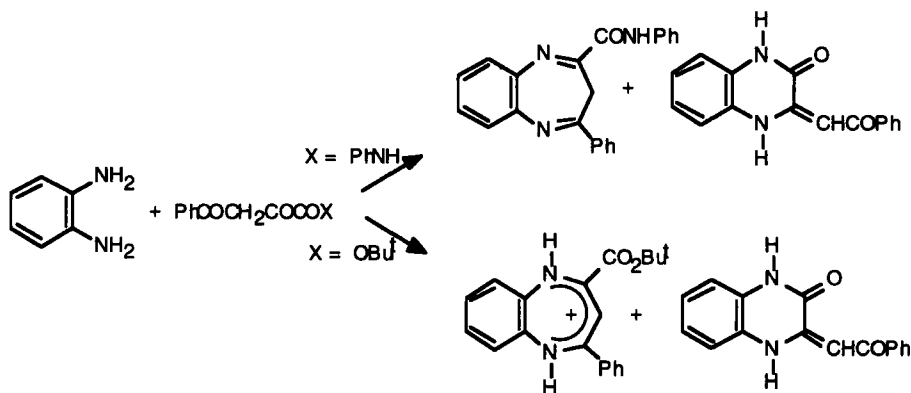
Mono-*N*-methyl-*o*-phenylenediamine reacts with acetylacetone to provide 1,2,4-trimethylbenzodiazepinium salts, but the yield is low, and it was not possible to isolate the base. This has also been ascribed to destabiliza-



SCHEME 5

tion of the ring-closed form due to steric hindrance between adjacent methyl groups (63JA3354). It was necessary to carry out the preparation in two steps. Using standard conditions only an anil, formed by condensation of the primary amino group with one carbonyl group of acetylacetone, was obtained, but when this imine was heated in benzene containing hydrogen chloride, and water was azeotropically removed from the reaction mixture, some benzodiazepinium chloride was obtained.

The reactions of several polyketones with *o*-phenylenediamine have been shown to provide benzodiazepines. Thus, triacetyl methane gives 2,4-dimethylbenzodiazepine (59JCS1132) and hexane-2,3,5-trione gives 2-acetyl-4-methylbenzodiazepine (69CB1643). Heptane-2,4,6-trione reacts with *o*-phenylenediamine in ethanol and in the presence of either acetic acid or potassium hydroxide (79BCJ2157; 93BSB565), or in xylene containing a few drops of hydrochloric acid (93BSB565), to give the product (10), which with aqueous mineral acid is hydrolyzed to a 2,4-dimethylbenzodiazepinium salt. This salt is formed directly from the reactants in ethanol-hydrochloric acid (Scheme 5).



SCHEME 6

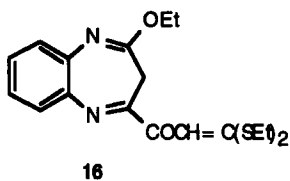
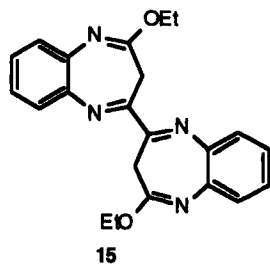
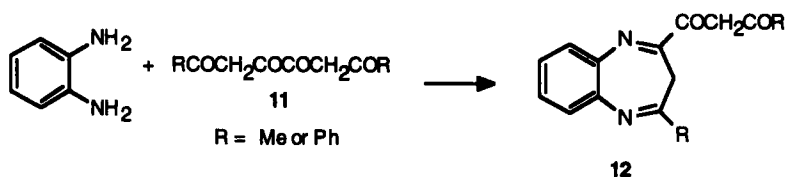


Condensation of aroylpyruvic acid anilides with *o*-phenylenediamine provided 2-phenyl-4-arylcarbamoylbenzodiazepines and a quinoxaline derivative (77JOU483; 77ZOR529; 78JOU156; 78ZOR169); an aroylpyruvic acid ester gave the same quinazoline derivative and 2-butoxycarbonyl-4-phenylbenzodiazepinium chloride; the latter benzodiazepinium salt rearranges to the quinoxaline in dioxan (78JOU156, 78ZOR169) (Scheme 6). Reaction of *o*-phenylenediamine with acetylpyruvic acid gave a product that was described as a phenazine derivative but could well have been 2-carboxy-4-methylbenzodiazepine [50LA(569)17].

The tetraketones (**11**) gave the benzodiazepines (**12**), which did not react with a further molecular equivalent of *o*-phenylenediamine to form bis(benzodiazepines) (58JCS4094) (Scheme 7).

The ketoketene acetals (**13**) and (**14**) reacted with *o*-phenylenediamine to give the benzodiazepines (**15**) and (**16**) respectively (62CB2172) (Scheme 7).

Several 2- and 2,3-disubstituted benzodiazepines have been prepared by reactions involving *o*-phenylenediamine and 3-ketoaldehydes/2-hydroxymethyleneketones (67JPR166; 70JOU450; 70ZOR450; 79MI1), and a



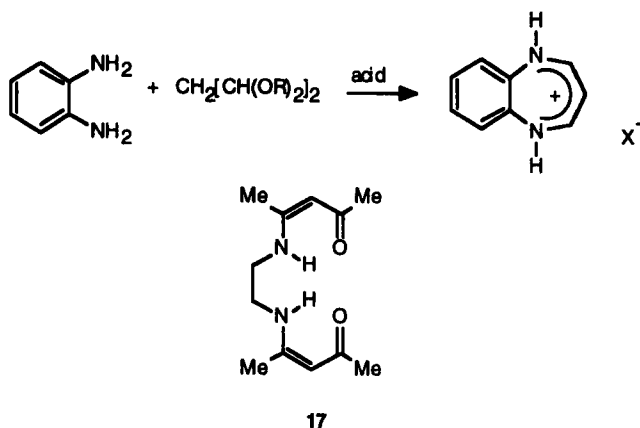
SCHEME 7

series of 2,3-cycloalkenobenzodiazepines was obtained starting from 2-formylcycloalkanones/2-hydroxymethylenecycloalkanones (63JPR117).

A number of 3-substituted benzodiazepines have been made starting from substituted malonaldehydes, including the following: 3-phenyl (27HCA 846; 62JPR156), 3-bromo (62JPR156), 3-nitro [52JCS2144; 56CI(L)765; 56JCS4731], 3-phenylazo (75HCA917), 3-diphenylmethylene (89CCC2721), 3-(4'-nitro-1'-pyrazolyl) (86IZV2392; 88CCC1529), and 3-(6'-chloro-2'-benzoxazolyl) (75IJC304).

Salts of the parent unsubstituted 1,5-benzodiazepine, which are red or purple solids, have been prepared by the reaction of *o*-phenylenediamine with malonaldehyde diacetals, either in ethanol-acetic acid-hydrochloric acid, methanol-perchloric acid (65JCS3785), or ethanol-hexafluorophosphonic acid (85IC2276, 85IC2281) (Scheme 8).

Condensation reactions between *o*-phenylenediamine and 1,3-dicarbonyl compounds in protic solvents are strongly pH dependent, and the best yields are obtained under slightly acidic conditions (51JCS3155; 59JCS1132; 65JCS3785; 76MI2). Thus, in aqueous solution the maximum yield of benzodiazepine was obtained from acetylacetone in solutions buffered to pH~5 (51JCS3155); the yield dropped to zero at pH greater than 8. In the reactions of aliphatic or alicyclic 1,2-diamines with 1,3-diketones, alternative products, e.g., (17), are obtained in weakly alkaline solution (56JCS2597). No such products have been isolated from the related condensation reactions involving 1,2-diaminoarenes, but an investigation of the production of 2,4-dimethylbenzodiazepine from acetylacetone and *o*-phenylenediamine in buffered aqueous solutions showed that there was a minimum yield at pH 6.0 and that the benzodiazepine was contaminated



SCHEME 8

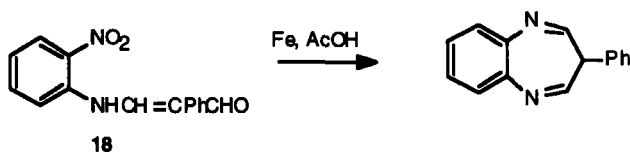
with another product that could not be obtained pure but whose IR spectrum was consistent with its being analogous to (17) (65JCS3785).

Condensation reactions between *o*-phenylenediamine and 1,3-diketones also proceed in aprotic solvents. Thus, alternative methods for the preparation of benzodiazepines have involved heating the hydrochloride of the diamine with a solution of the diketone in benzene (63JA3354), heating the diamine and diketone in dry xylene containing toluene-*p*-sulfonic acid (59JCS1132), and passing dry hydrogen chloride through an ethereal solution of the reactants (65JCS3785). In the latter method the benzodiazepinium dihydrochloride precipitates and is converted into the monoacid salt by addition of water. 2-Methyl-4-phenylbenzodiazepinium salts have also been prepared by the reaction of *o*-phenylenediamine with Schiff bases derived from benzoylacetone (85MI1).

Substituted *o*-phenylenediamines have also been used for the preparation of benzodiazepines, e.g., (65JCS3785; 69JOU171, 69ZOR175) (see also the preceding discussion). Pure samples of *o*-phenylenediamines, especially those having further electron-donating substituent groups attached to the ring, are sometimes difficult to obtain. To overcome this problem a modified procedure has been used in which an *o*-nitroamine was reduced by means of hydrazine hydrate in the presence of Raney nickel; immediately after decomposition of the excess of hydrazine hydrate the resultant solution of diamine was filtered directly into a solution of the diketone (65JCS3785). The diamine was thus protected from oxidation throughout its preparation by the excess of hydrazine present. A nitroamine has also been reduced catalytically to the diamine and added directly to the diketone (71CHE519, 71KGS556). 6-Phenylbenzodiazepine was prepared from the *o*-nitroamine derivative (18) by its reduction with iron and acetic acid or tin and hydrochloric acid (27HCA846) (Scheme 9).

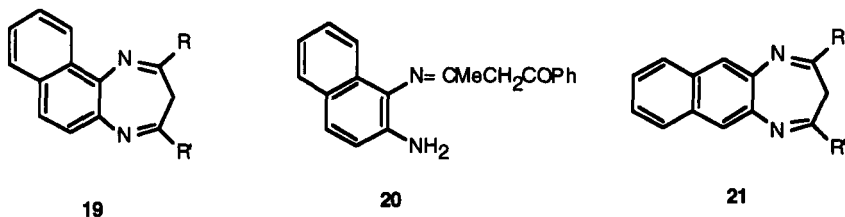
Bisbenzodiazepines have been prepared by condensation of the tetrahydrochlorides of 1,2,4,5-tetraminobenzene or 3,3',4,4'-tetraminobiphenyl with acetylacetone in the presence of a base (68JHC147).

Naphthodiazepines have been obtained from diaminonaphthalenes. 1,2-Diaminonaphthalene condenses with acetylacetone (54CB1801; 65JCS 3785), benzoylacetone (54CB1801), or dibenzoylmethane (54CB1801) in methanol-acetic acid, and addition of acid gives salts of the naphthodiaze-



SCHEME 9

pinines (**19**). In the case of benzoylacetone, a monoanil (**20**) could also be obtained if no acid were added. This anil was rapidly hydrolyzed with concomitant formation of a 2-methylnaphthimidazole, but if treated with acid was converted into the naphthodiazepine (**19**, R = Me, R' = Ph).



2,3-Diaminonaphthalene also reacts with the appropriate diketones in ethanol-acetic acid followed by addition of mineral acid to give naphthodiazepinium salts, which were converted by alkali into the naphthodiazepines (**21**, R = R' = Me; R = Me, R' = Ph; R = R' = Ph) (59CB2902; 65JCS 3785). If no acid is added, acetylacetone and benzoylacetone give anils corresponding to (**20**) but dibenzoylmethane does not condense at all (59CB2902). It appears that in the absence of acid catalysts, aryl ketones are insufficiently reactive to condense with the diaminonaphthalenes.

2,3-Amino-1,4-naphthoquinone only gave monoanils with 1,3-diketones, even in the presence of mineral acid (67JOU157, 67ZOR162).

## B. FROM $\beta$ -CHLOROVINYL CARBONYL COMPOUNDS

$\beta$ -Chlorovinylaldehydes (**22**) and  $\beta$ -chlorovinylketones (**23**) may be regarded as the acyl chlorides derived from the enol forms of 3-ketoaldehydes and 1,3-diketones.

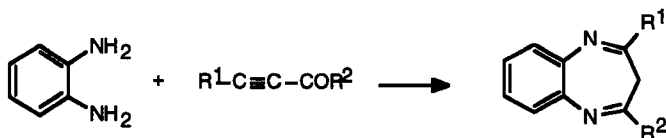


It is therefore not surprising that an alternative approach to the synthesis of benzodiazepines involves the reaction of  $\beta$ -chlorovinylcarbonyl compounds with *o*-phenylenediamine. In the first example methyl  $\beta$ -chlorovinyl ketone was used to obtain 5-methylbenzodiazepinium chloride (62 JPR163). An extensive investigation has been made of the use of  $\beta$ -chlorovinylaldehydes for the preparation of 2,3-substituted benzodiazepines (64ZC458; 67CB584). The preferred conditions for reaction were in

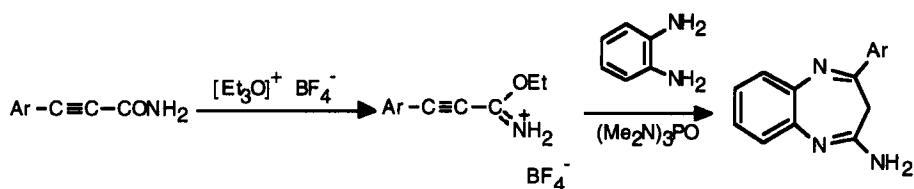
alcoholic hydrogen chloride. By this means a variety of 2-aryl-, 2,3-cycloalkeno- and 2,3-diarylbenzodiazepines were prepared. If no acid is present an uncyclized anil results, formed by condensation of one amino group with the aldehyde. Because  $\beta$ -chlorovinylaldehydes are themselves readily obtained by reaction of  $\alpha$ -methylene ketones with phosphoryl chloride and *N,N*-dimethylformamide or *N*-methylformanilide [see, *inter alia*, 58PCS227; 65CB3554; 70JCS(C)2484], this provides an attractive route to 2,3-disubstituted benzodiazepines. *N,N'*-dimethyl-*o*-phenylenediamine has served as the starting material to make 1,2,3,5-tetramethylbenzodiazepinium perchlorate, and *N*-methyl-*o*-phenylenediamine was used for making 1-methyl- and 1-methyl-2,4-diaryl-benzodiazepinium salts (67ZC456). Chlorovinylimines, formed by an initial condensation reaction between the aldehyde group and the primary amine groups, were shown to be intermediates in the latter cyclizations (67CB584).

### C. FROM $\alpha$ -ALKYNYL KETONES

Benzodiazepines and naphthodiazepines, and especially 2,4-diaryl derivatives, have been prepared, often in good yield, by combined Michael addition and condensation reactions of *o*-phenylenediamine and its substituted derivatives, *N*-methyl- and *N*-phenyl-*o*-phenylenediamines or 2,3-diaminonaphthalene, with  $\alpha$ -alkynyl ketones [72CHE1544; 72KGS1702; 72LA(755)24; 73KGS1421; 76OPP306; 78JOU156; 78LA741; 78ZOR169; 88MI2] (Scheme 10). These reactions have been carried out in ethanol or methanol, and in some instances in mixtures of either of these solvents with acetic acid. Amides (78JOU156, 78ZOR169) and esters (72CHE1544; 72KGS1702) of 2-arylbenzodiazepine-4-carboxylic acids have also been made in this way, starting from amides or esters of phenylethynylpyruvic acid. 2-Amino-4-arylbenzodiazepines have been prepared from arylpropynamides by the series of reactions shown in Scheme 11 (73JHC399; 81JHC1257). A key factor here appears to be the use of hexamethylphosphoric triamide (HMPA) as solvent; it is known to catalyze nucleophilic addition reactions.



SCHEME 10



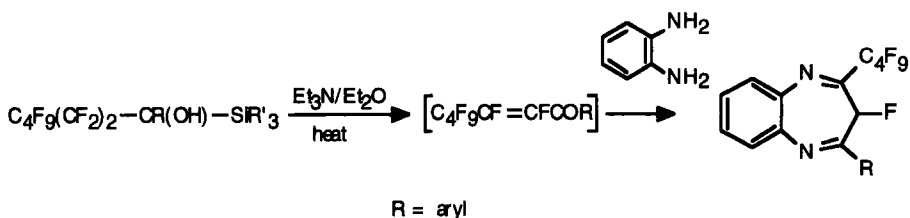
SCHEME 11

## D. SUNDRY METHODS

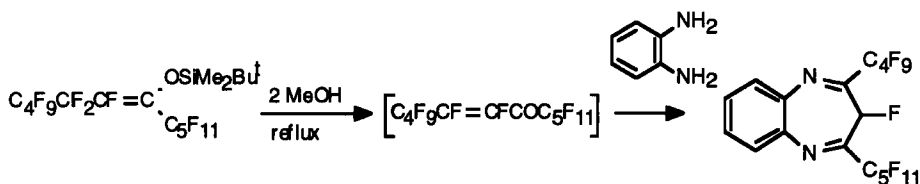
Benzodiazepines have been prepared from perfluoroenones, prepared *in situ*, for example Scheme 12 (94TL4357). This reaction obviously closely resembles the preparative method starting from ynones but, in addition to nucleophilic addition and condensation reactions, elimination of hydrogen fluoride is also involved.

*o*-Phenylenediamine has also been found to react with perfluoroalkenes to give fluorinated derivatives of benzodiazepine (79MI1; 80JFC75) (Scheme 13).

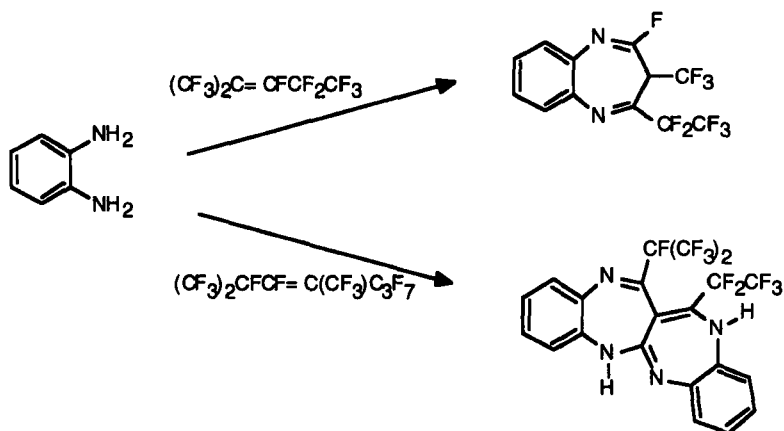
Vinamidinium salts are derivatives of 1,3-dicarbonyl compounds and undergo attack by nucleophiles [76AG496, 76AG(E)459]. In the case of 2,4-unsubstituted vinamidinium salts, nucleophilic substitution of the terminal amino groups may ensue but, if there are substituents at C-2 and 4 that can act as good leaving groups, they, rather than the terminal amino groups, may undergo substitution. Examples of each of these patterns of behavior



R = aryl



SCHEME 12

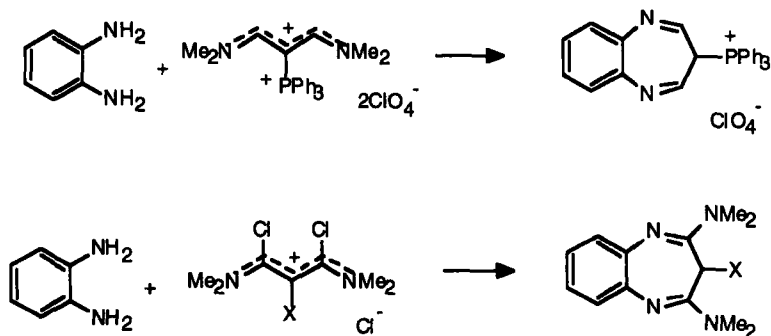


SCHEME 13

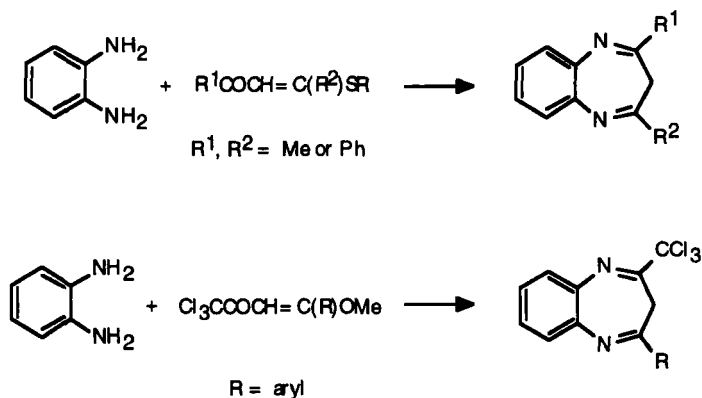
have been recorded in reactions of *o*-phenylenediamine with vinamidinium salts [73AG837, 73AG(E)806; 78BSB391; 82AG559, 82AG(E)543], (e.g. Scheme 14).

Vinamidines are examples of push-pull alkenes, and other push-pull alkenes  $\text{R}^1\text{COCR}^2=\text{CR}^3\text{X}$  ( $\text{X} = \text{SR}, \text{OR}$ ) also react with *o*-phenylenediamine to give benzodiazepines, e.g., Scheme 15 (85JHC405; 96TL9155).

Microwave irradiation has been used to promote reactions between the keto-enol ethers  $\text{CF}_3\text{COCR}=\text{CHOBu}^t$ ,  $\text{R} = \text{H}$  or  $\text{COCF}_3$ , and *o*-phenylenediamines in solution in xylene (96TL2845; 97T5847). These reactions did not proceed satisfactorily in the absence of the microwave irradiation. The  $^1\text{H}$  NMR spectra indicate that the products have conjugated vinamidine structures in the diazepine moiety rather than the usual diimine structure. Of the two possible tautomers that could be formed, in each case



SCHEME 14

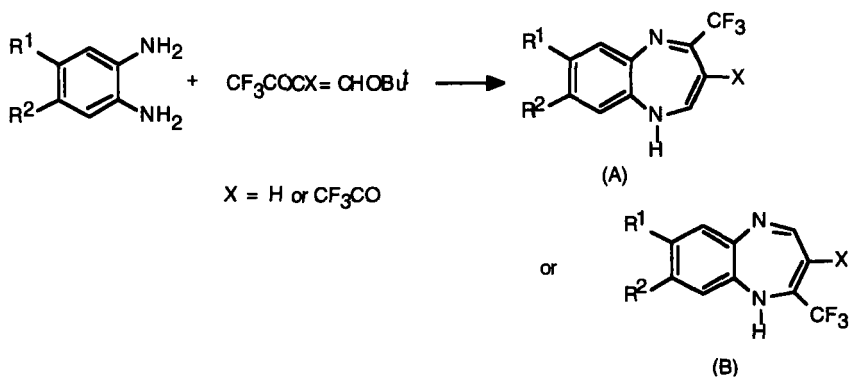


SCHEME 15

only one was observed (Scheme 16). When  $R', R^2 = \text{H, Me, or Cl}$ , isomer (A) is formed, but when  $R' = \text{H}$  and  $R^2 = \text{NO}_2$  or  $\text{COPh}$ , the alternative isomer (B) resulted. It would appear that, in the absence of strongly electron-withdrawing substituents in the benzene ring, the trifluoromethyl group strongly stabilizes (A) with respect to (B), but that this effect is nullified and overridden by electron-withdrawing groups that favor formation of tautomer (B).

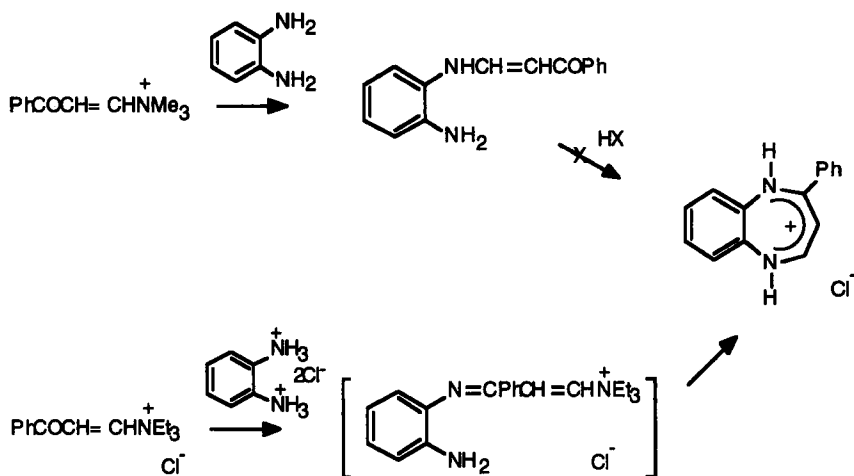
The ketoenammonium salt  $\text{PhCOCH}=\text{CHN}^+\text{Me}_3 \text{ Cl}^-$  reacts with *o*-phenylenediamine to give 2-benzoylvinylaminoaniline, but a triethylammonium analog reacted with the dihydrochloride of the diamine to give a benzodiazepinium salt (78JPR659) (Scheme 17).

Chromone-3-aldehyde reacts with *o*-phenylenediamine to give an annelated benzodiazepine. This also involves condensation and Michael addi-



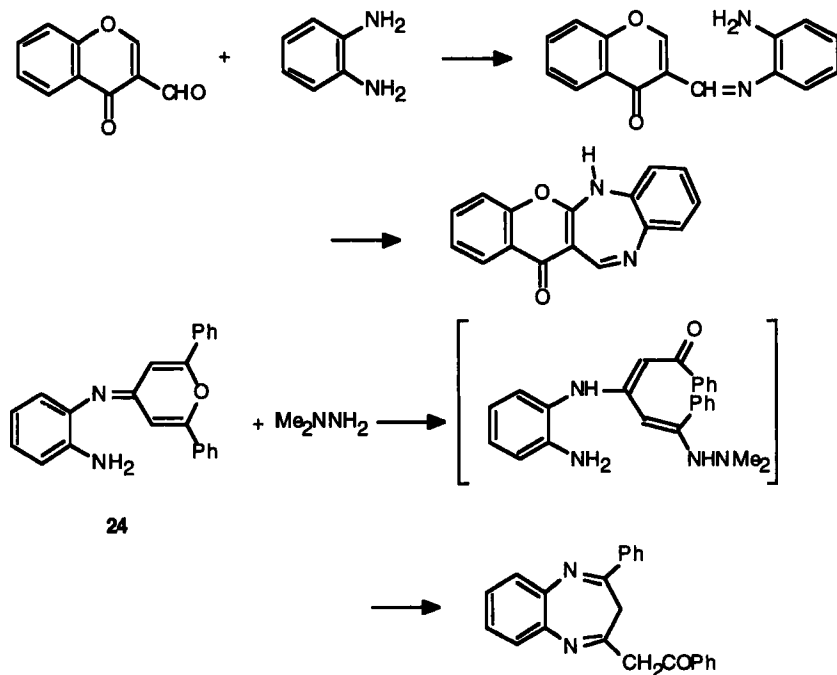
SCHEME 16





SCHEME 17

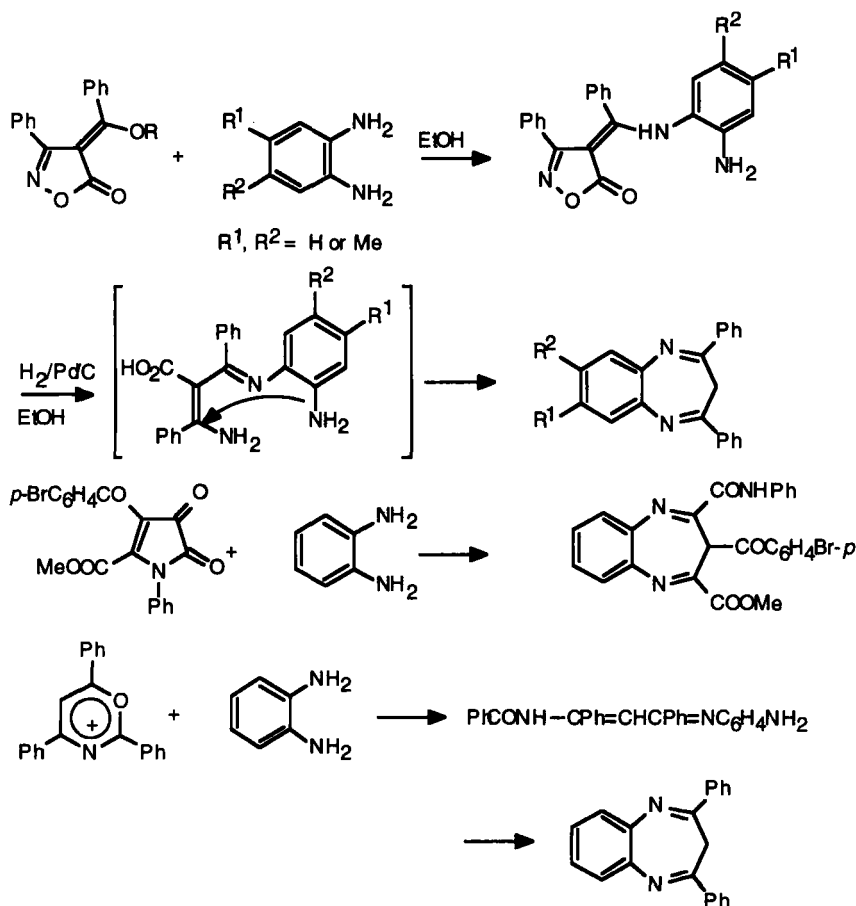
tion reactions of a push-pull alkene, but these must be followed by a dehydrogenation step; it was suggested that this results from aerobic oxidation (80S701) (Scheme 18).



SCHEME 18

On treatment with ammonia, pyridine, or, best, *N,N*-dimethylhydrazine, the pyrone derivative (**24**) is converted into 2-phenacyl-4-phenylbenzodiazepine (**74JHC1065**). It was suggested that attack by dimethylhydrazine at the 2-position of the pyrone ring was followed by ring opening and recyclization to form a 7-membered ring (Scheme 18). Reaction of 4-chloro- or 4-nitro-*o*-phenylenediamine with 4-methoxy-2,6-diphenylpyrylium perchlorate followed by dimethylhydrazine gave 2-benzoyl-7-chloro or nitro-4-phenyl-benzodiazepine (**74JHC1065**).

There are a number of other examples of reactions involving opening of 5- or 6-membered rings by *o*-phenylenediamine followed by recyclization to form 7-membered rings. Examples involving isoxazolones (**73CB332**) pyrrolidinediones (**88ZOR1565**; **89ZOR1748**) and oxazinylium salts (**81BCJ2387**) (Scheme 19).



SCHEME 19

When the di-indolyltetrahydroquinoxaline derivative (**25**) is heated with an ethanolic solution of potassium hydroxide (10%) in diethyleneglycol, it is converted into a 2,3-di-indolyl-4-methylbenzodiazepine (85KGS132, 85KGS1551) (Scheme 20).

The tris-*t*-butylthiocyclopropenium cation undergoes nucleophilic attack by *o*-phenylenediamines with concomitant ring opening, leading to the formation of 2,3-bis-*t*-butylthiobenzodiazepines (89T3217) (Scheme 20).

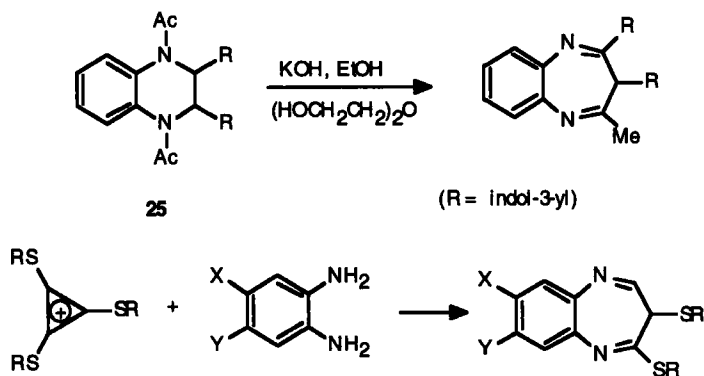
Some other methods that have been used for the preparation of alkylthio- and amino-benzodiazepines are mentioned in Section VII, which deals specifically with such derivatives.

Claims that 2,3,4-triphenylbenzodiazepine is obtained by condensation of *o*-phenylenediamine with three molecules of benzaldehyde (34RZC 1312; 55MI1) were later shown to be incorrect (70IJC790); the products were in fact benzimidazoles.

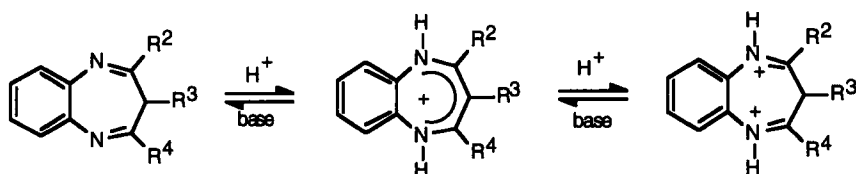
In concluding this section it may be noted that attempts to obtain 1,5-benzodiazepines by dehydrogenation of either 2,3-cyclohexano-2,3-dihydro-1,4-diazepines or of 2,3-benzotetrahydro-1,4-diazepines were unsuccessful (65JCS3785). Thus, there is obviously no great energetic driving force toward the formation of 1,5-benzodiazepines; this is in accord with the lack of any marked stabilization of the 7-membered ring in these benzodiazepines.

### III. Structure

1,5-Benzodiazepines are converted by acid into, in turn, monocations and dications (Scheme 21). Most 1,5-benzodiazepines exist in the diimine (3H) form shown, rather than as vinamidines, the isomeric 1H form, although some 2-trifluoromethyl derivatives have been assigned conjugated vinami-



SCHEME 20



SCHEME 21

dine structures on the basis of their  $^1\text{H}$  NMR spectra (96TL2845; 97T5847), and 1-substituted derivatives must inevitably adopt a conjugated structure. The conjugated form, which would have eight  $\pi$ -electrons associated with the 7-membered ring, is electronically an analog of benzocyclooctatetraene. Annular conjugation around either the diazepine ring or the overall periphery makes no positive contribution to the stability of the system, whereas electronic interaction between the benzene ring and the two imino groups in the imino form does.

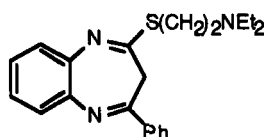
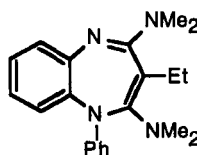
With a few exceptions the bases are colorless or pale yellow, as are the dications, which must exist as bisiminium salts. In contrast the monocations are intensely colored, commonly purple or blue. Formation of the monocation involves setting up a stable 6- $\pi$ -electron vinamidinium system; such systems have stabilization energies of the order of  $20 \text{ kcal} \cdot \text{mol}^{-1}$  [72CI(L)335]. It has been noted that when a solution of the purple 2,4-dimethylbenzodiazepinium hydrochloride was basified, a yellow solution resulted that turned colorless after a few seconds. This was attributed to initial formation of the conjugated base (2), which rapidly tautomerized to the usual diimine form (40HCA1147).

There is energetic advantage in generating the stabilized vinamidinium system, but there is disadvantage if it interacts appreciably with the 6- $\pi$ -electron system of the benzene ring. To minimize such interaction, the bonds linking the nitrogen atoms to the benzene ring are long for aryl C-N bonds. Their calculated (MNDO) bond order is 0.941, whereas bond orders for the vinamidinium system are in accord with its having a largely delocalized structure (82TL4379). The situation here, where two 6- $\pi$ -electron systems attempt to stand at arms' length from each other, resembles that which obtains in the case of biphenylene, wherein two benzenoid rings are linked by two abnormally long C-C single bonds (82TL4379; 84T4455). In both the benzodiazepinium cation and biphenylene, the bonds common to two rings are longer and have lower bond orders than the other bonds in the benzene rings. In each case this serves to decrease the possibility of a  $4n$  circuit of  $\pi$ -electrons developing in the nonbenzenoid ring.

The structures of the bases and salts were originally based on spectroscopic evidence (see Section IV), but more recently a number of X-ray structure determinations have been carried out. Studies were made of 2,4-

dimethylbenzodiazepinium chloride [76AX(B)622] and hexafluorophosphate (91ZK148, 91PC1), the hydrochloride of the 2,4-dimethylnaphthodiazepine (**21**,  $R = R' = \text{Me}$ ) [93AX(C)156], and of mixed crystals consisting of 2,4-dimethylbenzodiazepinium and benzene-1,2-diammonium cations and chloride anions (81CSC429). In these mixed crystals the structure of the benzodiazepinium cations closely resembles that in the other benzodiazepinium salts, except that there is slight folding (ca.  $11^\circ$ ) of the 7-membered ring through C-2 and C-4; the other examples all have nearly planar structures. In all these cations the bonds linking the nitrogen atoms to the benzene ring are long ( $\sim 1.425 \text{ \AA}$ ) for  $sp^2$  N-C(aryl) bonds, confirming the tendency for the 6- $\pi$ -delocalized benzenoid and vinamidinium systems to remain as isolated systems. Bond lengths in the vinamidinium system, C-C =  $1.375\text{--}1.380 \text{ \AA}$  and C-N =  $1.323\text{--}1.334 \text{ \AA}$ , are in accord with the delocalized nature of the system and are similar to those observed in 2,3-dihydro-1,4-diazepinium cations, although the latter have slightly longer C-C bonds ( $\sim 1.395 \text{ \AA}$ ) and slightly shorter C-N bonds ( $1.315 \text{ \AA}$ ) [93AHC(56)1]. The ring angles in the 7-membered rings are similar to those in dihydrodiazepinium cations; they are markedly greater ( $125\text{--}131^\circ$ ) than the  $120^\circ$  normal for  $sp^2$  atoms. In the benzene rings the bond shared with the 7-membered ring is the longest and the 7,8-bond is the shortest [76AX(B)622; 81CSC429]; this is also in accord with calculated (MNDO) bond orders (82TL4379).

X-ray crystal structures have also been reported on two 1,5-benzodiazepine bases, the 2,4-disubstituted base (**26**) (88JHC305) and the N-substituted base (**27**) (79CSC981), wherein a diimine structure is not possible.

**26****27**

In (**26**) both the bond common to the two rings ( $1.35 \text{ \AA}$ ) and the bonds linking the nitrogen atoms to the benzene ring ( $1.40 \text{ \AA}$ ) are shorter than the corresponding bonds in the salts, suggesting that there is more electronic interaction between the two rings in the bases, between the benzene ring and the imine groups. The latter have bond lengths of  $1.24$  and  $1.28 \text{ \AA}$ , consistent with their designations as double bonds. The C-2-C-3 and C-3-C-4 bond lengths are  $1.48$  and  $1.49 \text{ \AA}$ ; i.e., they are single bonds. The internal bond angle at C-3 is  $107^\circ$ , and the mean internal bond angles are  $120^\circ$  at C

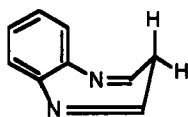
2,4 and  $121^\circ$  at the nitrogen atoms. The diazepine ring has a rigid boat conformation and as a result achieves conformational chirality. The two enantiomers, which are contained in the same asymmetric unit of the crystal, interchange by ring reversal.

The 7-membered ring in (27) has a distorted boat shape. Bond lengths alternate along the vinamidine chain, N-1-C-2 = 1.42 Å, C-2-C-3 = 1.32 Å, C-3-C-4 = 1.52 Å, C-4-N-5 = 1.29 Å, as expected. The bonds around the benzene ring are all of similar length, average = 1.40 Å

#### IV. Spectra

The IR spectra of 2,4-dialkyl- and 2,4-diaryl-benzodiazepines are in accord with their diimine structures in that they show no peaks attributable to NH groups but do indicate the presence of a methylene group (58JCS4094; 59JCS1132; 62JPR156). They have signals at  $\sim 1600\text{ cm}^{-1}$  derived from the C=N bonds (62JPR156; 78LA741).

The diimine structure is also apparent from their  $^1\text{H}$  NMR spectra (59JCS1423; 65CB2701; 65SA1095), which show the presence of a methylene group at C-3. This provides a signal at  $\delta \sim 2.75$ , but, if flanked by aryl groups, at  $\delta \sim 3.1\text{--}3.7$ , the downfield shift resulting from shielding by the vicinal aryl groups (73T147; 78LA741). At normal operating temperatures the methylene signals commonly appear as singlets, but at lower temperatures they give rise to double doublets (67CB335). These results demonstrate that the benzodiazepine molecules take up boat conformations (28) in solution but are inverting rapidly at room temperature.



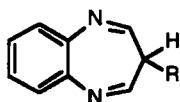
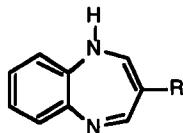
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For the compounds that were studied,  $\Delta G^\ddagger$  for inversion was in the range of 11 to 13  $\text{kcal} \cdot \text{mol}^{-1}$ . Phenyl substituents at positions 2 and 4 cause an increase in  $\Delta G^\ddagger$  compared with 2,4-methyl groups; this was ascribed to their having greater steric requirements in the transition state (67CB335).

Conversion of a benzodiazepine into its monocation results in the disappearance of the methylene signal in the  $^1\text{H}$  NMR spectrum and its replacement by a methine signal at  $\delta \sim 4.0\text{--}4.5$  [74KGS828; 76JCS(P1)2353; 85IC2276, 85IC2281]. Further protonation to form a dication (5) takes

place at the 3-position, resulting in the reappearance of a methylene signal, at  $\delta \sim 4.7$ , confirming that the site of protonation of the monocation is C-3 rather than on nitrogen (65CB2701; 74KGS828). However, both the 3-H and N-H undergo hydrogen-deuterium exchange in deuteriosulfuric acid (65CB2701).

Also in accord with their diimine structure, benzodiazepines have absorption bands in their electronic spectra at  $\sim 260$  nm, similar to that of benzyldieneaniline (59JCS1132; 85IC2276, 85IC2281). Certain benzodiazepines that have electron-withdrawing substituents, i.e., nitro [52JCS2144; 56CI(L)765], phenyl (27HCA846; 62JPR156), and bromo (62JPR156) at C-3 are red. Their IR spectra have no signals corresponding to NH groups, indicating that they exist in the diimine form (**29**). It is difficult to see how such a structure could of itself lead to absorption at  $\sim 500$  nm. Possibly trace amounts of the tautomer (**30**), stabilized by push-pull electronic interaction between the donor NH group and the acceptor 6-substituent but insufficient to provide an obvious NH signal in the IR spectrum, are present. This could open the way for more extended conjugation through the molecule, possibly supplemented by charge-transfer interactions.

**29****30**R = NO<sub>2</sub>, Ph Br

In the benzodiazepinium monocations the intensities of the absorption bands at  $\sim 260$  nm are increased enormously compared to those in the bases, and there are also bands at  $>500$  nm, which are responsible for the intense color of these salts (59JCS1132; 65JCS3785; 71MI1; 78JPR659). The color and electronic spectra have been discussed in terms of configuration analysis and inspection of the key orbital interactions between the constituent molecular fragments, namely the aryl and vinamidinium groups (78JPR361). It has been suggested that these long-wavelength absorptions are associated with  $n\text{-}\pi^*$  transitions and that charge-transfer interactions are also involved (71MI1; 78JPR361); this is supported by the fact that change of solvent from methanol to dimethyl sulfoxide causes a red shift for these maxima (71MI1). In the crystals the stacking of the flat cations may well also contribute to the intense colors [76AX(B)622].

In the dications the vinamidinium system is lost and a methylene group is reinstated at C-6. In keeping with this the long-wavelength bands are ab-

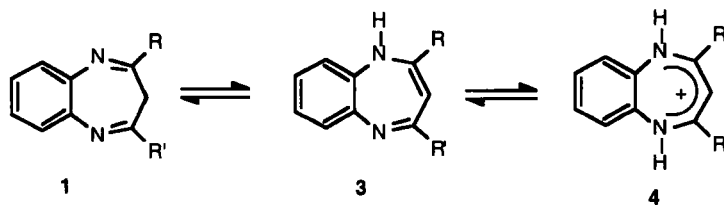
sent in their electronic spectra; they have bands with maxima at  $\sim 260$  nm, comparable to those in the corresponding bases (65JCS3785; 71MI1).

In their mass spectra, benzodiazepines have been reported to show the molecular ion peak as the base peak and also strong  $(M^+ + 1)$  peaks (78LA741; 82JHC107). The main fragmentations involve skeletal rearrangements; benzimidazole cations are often apparent, as are indole and quinoxaline ions (78FES885; 78LA741).

## V. Basicity: Possible Use as Indicators

1,5-Benzodiazepines are very much weaker bases than are 2,3-dihydro-1,4-diazepines. Their monocations also need weaker acids to convert them into dications than do dihydrodiazepinium cations. The  $pK_a$  values for the monocation  $\rightleftharpoons$  base equilibria are  $\sim 5$ ; aryl-substituted benzodiazepines are weaker bases than alkyl-substituted analogs [40HCA1147; 63JA3354; 66MI1; 72CI(L)335; 80MI2]. The  $pK_a$  value for the monocation  $\rightleftharpoons$  dication equilibrium is  $\sim -1$  (40HCA1147, 40HCA1162). A number of factors influence the difference between these benzodiazepines and the related 2,3-dihydro-1,4-diazepines, namely the less stabilized nature of the benzodiazepinium cation compared to the strongly stabilized dihydrodiazepinium cation, interaction in the benzodiazepine base between the nitrogen atoms and the benzene ring, and the necessity for tautomeric change of the benzodiazepine base to the less favored conjugated form on monocation formation. This last factor complicates the situation concerning the equilibrium  $(1) \rightleftharpoons (4)$ , which is really a combination of two equilibria:  $(1) \rightleftharpoons (3) \rightleftharpoons (4)$  (40HCA1162; 65JCS3785). A  $pK_a$  value of 9 has been assigned to the equilibrium  $(3) \rightleftharpoons (4)$  (40HCA1162) (Scheme 22).

Because of the striking color change between the bases (1) and monocations (4), it has been suggested that they could be useful indicators in acid-base titrations. A number of 2,4-disubstituted derivatives have been suggested for use over the pH range 5–9 (80MI2), and certain 3-aryl-



SCHEME 22



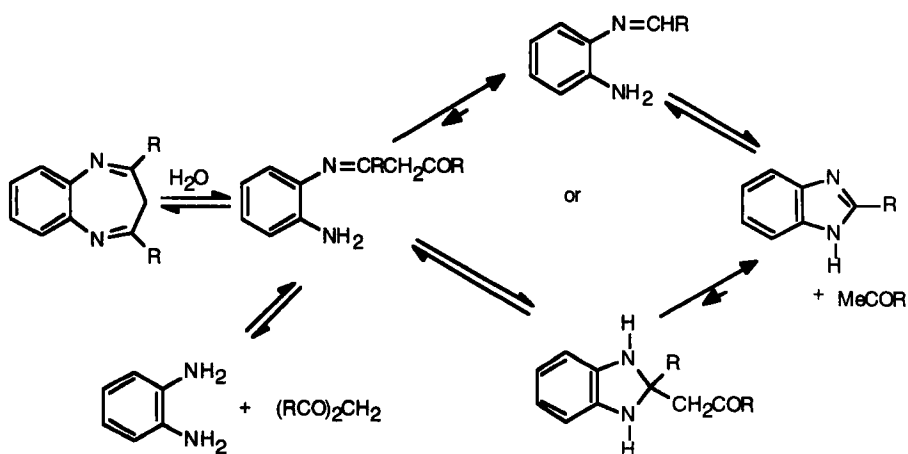
sulphonyl-2-alkyl or -aryl-4-methyl derivatives for the pH range 5–7 (75MI4; 78MI1).

## VI. Reactions

### A. HYDROLYSIS: RING-CONTRACTION REACTIONS

Benzodiazepines and benzodiazepinium salts undergo ring contraction to give benzimidazoles when heated in aqueous solution (07CB955; 59JCS1132; 63JA3354; 63JPR117; 65JCS3785, 65JOU159, 65ZOR163). This presumably proceeds via opening of the diazepine ring to form a monoanil, with subsequent hydrolytic cleavage and closure to form an imidazole ring (Scheme 23). Alternatively, further hydrolysis of the monoanil may lead to formation of a diamine and a 1,3-dicarbonyl compound.

In the formation of a benzimidazole the steps involving loss of a methyl ketone, which are essentially irreversible, control the course of the reaction. Examples of such ring-contraction reactions are the formation of 2-methylbenzimidazole and acetone from 2,4-dimethylbenzodiazepine and its salts (07CB955; 59JCS1132; 65JCS3785) and of a mixture of acetone, acetophenone, 2-methyl-, and 2-phenylbenzimidazoles from 2-methyl-4-phenylbenzodiazepine (07CB955). The same ring contractions also ensue when aqueous solutions of benzodiazepines or their salts are kept at room temperature. It seems likely that in the case of solutions of the salts, some free base, present in equilibrium with the cation, may be the species in-



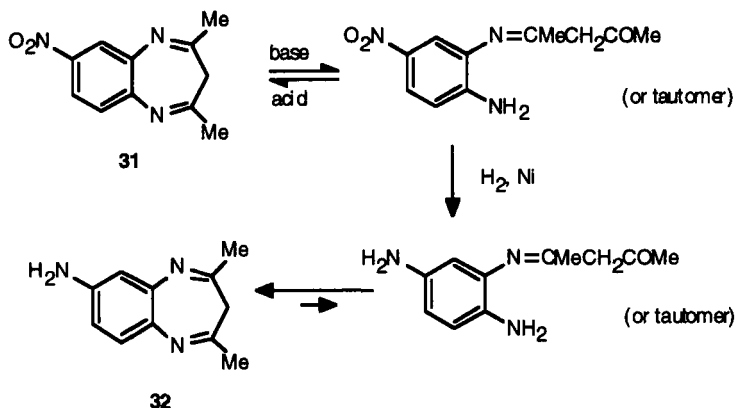
SCHEME 23

involved in hydrolysis, because addition of traces of mineral acid greatly retards the rate of formation of benzimidazole (65JCS3785). Solutions in methanol are much more stable, and solutions in methanol containing small amounts of mineral acid apparently keep indefinitely (65JCS3785).

2,3-Disubstituted benzodiazepines appear to be more readily hydrolyzed than 2,4-disubstituted analogs (67CB584). Hydrolysis involves attack at the 2- or 4-positions, and this is easier in the absence of a blocking substituent.

The concentration of ring-opened monoanil in solution can only be small, because in the case of a number of benzodiazepines none could be detected spectroscopically (59JCS1132). However, the presence of electron-withdrawing substituents in the benzene ring assists nucleophilic attack at the 2- or 4-position, and in the case of 2,4-dimethyl-7-nitrobenzodiazepine (**31**), the formation of the monoanil in methanolic alkali could be readily detected spectroscopically (65JCS3785; 69JOU171, 69ZOR175). Addition of acid resulted in instant reformation of the benzodiazepine (65JCS3785). Reduction of the anil with Raney nickel as catalyst led to the formation of 7-amino-2,4-dimethylbenzodiazepine (**32**) (69JOU171, 69ZOR175); presumably the 4-nitro group is reduced to an amino group, which activates the 1-amino group to undergo ring closure with re-formation of the diazepine ring (Scheme 24). Both naphtho[1,2]- and naphtho[2,3]-diazepinium salts undergo similar ring-contraction reactions to form naphthimidazoles when heated in aqueous solution (54CB1801; 59CB2902).

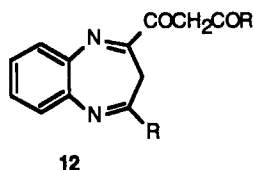
Hydrolysis of 3-acylbenzodiazepines in acidic conditions may lead to hydrolytic removal of the acyl group. Thus, treatment of 3-benzoyl-2,4-diphenylbenzodiazepine with aqueous hydrochloric acid provides 2,4-diphenylbenzenediazepinium chloride and benzoic acid; some 2-phenylbenzimidazole and dibenzoylmethane are also formed (71MI2). The



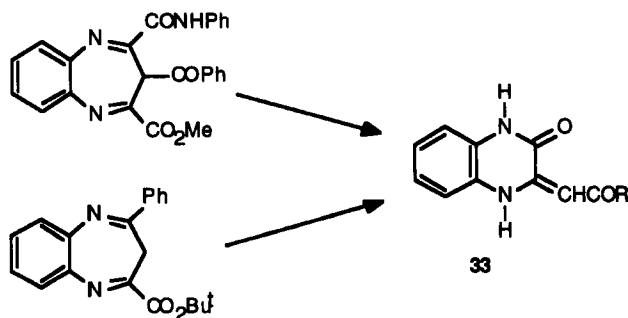
SCHEME 24

formation of 2,4-dimethylbenzodiazepine from *o*-phenylenediamine and triacetylmethane (59JCS1132) could involve loss of an acetyl group either before or after condensation.

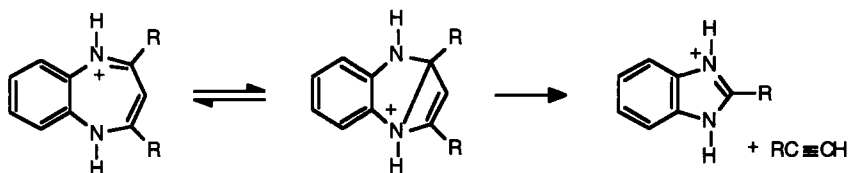
Further evidence for the trace amounts of ring-opened products from benzodiazepines in aqueous solution comes from observations that such solutions can participate in reactions of the dicarbonyl compound and diamine from which the benzodiazepine is derived. Thus, diacetyl reacts with solutions of benzodiazepines to give quinoxalines derived from the diamine fragment [57CI(L)466; 59JCS1132]. Similarly, with phenylhydrazine, solutions of benzodiazepines form pyrazoles derived from the dicarbonyl fragment; for example, 2,4-dimethylbenzodiazepine gives rise to 3,5-dimethyl-1-phenylpyrazole [07CB955; 57CI(L)466; 59JCS1132]. The benzodiazepine (**12**, R = Ph) gives 1,3,1',3'-tetraphenyl-5,5'-dipyrazolyl, but its methyl analog (**12**, R = Me) reacts only in the side chain to form a 2-methyl-4-pyrazolylbenzodiazepine (58JCS4094). The formation of the quinoxalone derivatives (**33**) from 2-(phenylcarbamoyl)-3-aryl-4-methoxycarbonyl- (88ZOR2234) or 2-phenyl-4-*t*-butoxycarbonylbenzodiazepinium salts (78JOU156, 78ZOR169) also involves ring-opening and succeeding ring-closure reactions (Scheme 25).



Distillation of solid benzodiazepinium salts may also lead to the formation of a ketone and a benzimidazolium salt (65JCS3785). A number of benzodiazepinium salts contain water of crystallization, and this, or adsorbed water, can presumably participate in the reaction. In the absence of



SCHEME 25



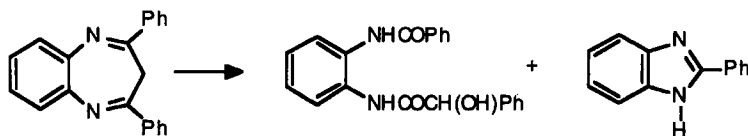
SCHEME 26

any such water, a reaction sequence as above could be invoked (Scheme 26). It is possible that some of the quoted melting points of benzodiazepinium salts are in fact those of the benzimidazolium salts, interconversion having taken place at a lower temperature.

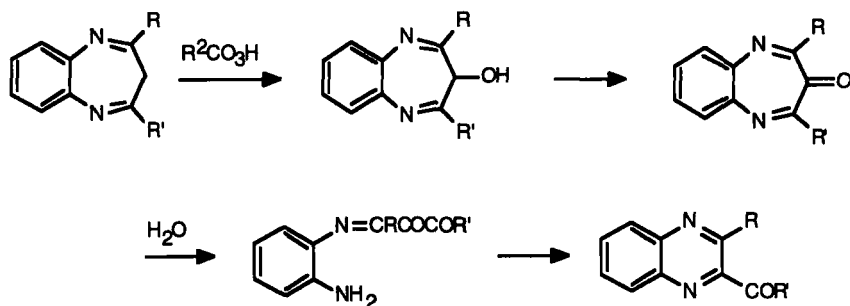
## B. OXIDATION

When 2,4-dimethylbenzodiazepine is treated with peracids, it undergoes ring contraction to form 2-acetyl-3-methylquinoxaline [57CI(L)466; 59JCS1132; 59JCS1423; 70BCJ1496]. Similarly 2-methyl-4-phenylbenzodiazepine is oxidized to 2-acetyl-3-phenylquinoxaline (70BCJ1496), but 2,4-diphenylbenzodiazepine gives *o*-(benzoylamino)- $\alpha$ -hydroxyphenylacetanilide and 2-phenylbenzimidazole, but not a quinoxaline (70BCJ281, 70BCJ1496) (Scheme 27). It has been suggested that both types of oxidation initially involved attack at the 3-position to form a 3-hydroxy derivative (59JCS1132; 70BCJ281; 70BCJ1496). This is oxidized further to a 3-oxo derivative, which undergoes ring opening followed by ring closure to give a quinoxaline that, in the case of the diphenyl compound, may then suffer oxidative cleavage (Scheme 28).

Solutions of benzodiazepines in benzene or acetic acid are oxidized by oxygen when irradiated with a high-pressure mercury arc. Ring contraction to give quinoxalines again ensues. In benzene hydrolytic cleavage is ruled out and an alternative mechanism involves a photolytic norcaradiene-type rearrangement of the intermediate to a quinoxaline (70BCJ1496) (Scheme 29).



SCHEME 27



SCHEME 28

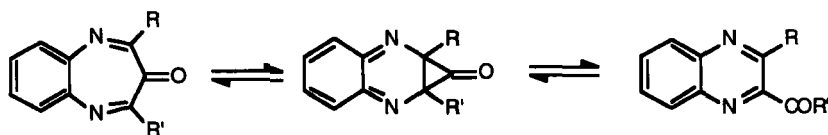
When a low-pressure mercury arc was used, 2,4-dimethylbenzodiazepine again gave a quinoxaline derivative whereas 2,4-diphenylbenzodiazepine gave low yields of *o*-bis(benzoylamino) benzene and 2,4-diphenylbenzodiazepin-3-one (68BCJ2543).

Oxidation of 2,4-dimethylbenzodiazepine with iron(III) chloride led to the formation of 2,3-diaminophenazine [57CI(L)466].

Oxidation of 2-amino-3-cyanobenzodiazepinium chloride with hydrogen peroxide in the presence of peroxidase as a catalyst gave benzimidazole, which, unlike the benzodiazepine, was fluorescent, and this reaction has been applied to the determination of hydrogen peroxide by fluorimetry (80CPB2325).

### C. HYDROGENATION

2,4-Dimethylbenzodiazepine was reduced catalytically, providing a mixture of *cis*- and *trans*-2,4-dimethyltetrahydrobenzodiazepines (59JCS1423). A naphtho[2,3]diazepine has also been reduced catalytically to a tetrahydronaphthodiazepine (59CB2902), but a naphtho[1,2]diazepine was reduced only very slowly over Raney nickel (54CB1801). 2,3-Dimethyl-7-nitro-1,5-benzodiazepine was reduced catalytically with Raney nickel to give the corresponding aminobenzodiazepine without reduction of the diazepine ring (69JOU171). When 2,4-dimethylbenzodiazepine was heated



SCHEME 29

with lithium aluminium hydride in refluxing tetrahydrofuran it was recovered unchanged (65JCS3785), but a number of benzodiazepines have been reduced in good yield to tetrahydro derivatives by sodium borohydride; 2,4-disubstituted benzodiazepines were converted into *cis*-disubstituted products (74IJC498; 75MI2, 75MI3). An intermediate dihydro derivative has also been isolated. 2-Amino-3-cyanobenzenediazepinium chloride was reduced by sodium borohydride to give a mixture of 2,3-dihydro- and 2,3,4,5-tetrahydro-3-cyanobenzodiazepines. It was suggested that deamination preceded reduction and was brought about by nucleophilic attack by hydride ions (81CPB1165). Only 3-ethoxycarbonyl-2,3-dihydrobenzodiazepine was obtained by reduction of the 2-amino-3-ethoxycarbonyl analog. Attempted reduction of 2,4-dimethylbenzodiazepine using sodium and ethanol provided only intractable tars (65JCS3785).

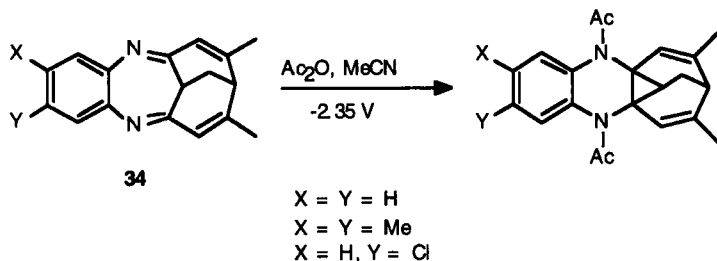
The fused-ring benzodiazepines (**34**) have been reductively acetylated electrochemically in acetonitrile at  $-2.35$  V; the products were cyclopropanotetrahydroquinoxalines [79JCS(CC)761] (Scheme 30).

## D. REACTIONS WITH ELECTROPHILES

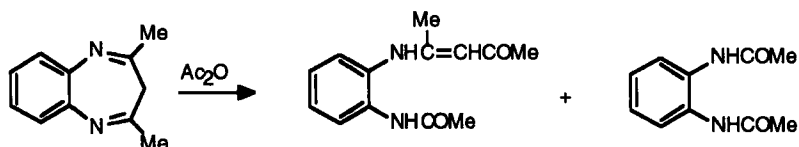
### 1. Acylation

Reaction of 2,4-dimethylbenzodiazepine with acetic anhydride led to the formation of ring-opened acetylated products (70CHE1061, 70KGS1135) (Scheme 31). When 7-amino-2,4-dimethylbenzodiazepine was treated with acetic anhydride, acetylation took place solely at the 7-amino group if only one molecular equivalent of anhydride was used, but excess acetic anhydride led to ring-opened products similar to the preceding (70CHE1061, 70KGS1135).

An *N*-acetylated product, whose formation involved conversion of the diimine structure into a vinamidine, could be obtained from benzodiazepine



SCHEME 30



SCHEME 31

(35), but if (35) was treated with an acyl chloride and triethylamine at low temperature only the phenolic group was attacked (77AP964) (Scheme 32).

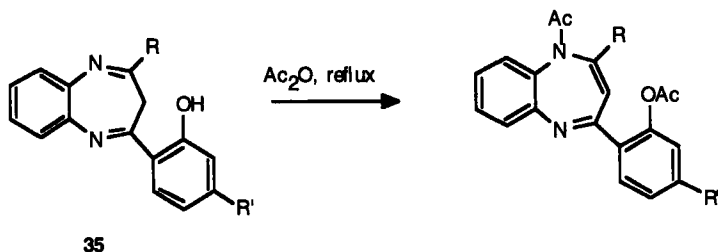
It was reported that 2,4-dimethylbenzodiazepine was mono-*N*-tosylated by toluene-*p*-sulfonyl chloride in pyridine (65JCS485), but the structure of the product has been questioned (91 C209).

## 2. Alkylation

The imine groups in benzodiazepines could increase the acidity of the hydrogen atoms attached to C-3 or to methyl substituents at C-2 and C-4, and thus these sites might be susceptible in basic conditions to attack by alkyl halides. 2,4-Dimethylbenzodiazepine reacted with iodomethane and sodium amide in liquid ammonia to give 2,3,4-trimethylbenzodiazepine (59JCS1132). The site of reaction was confirmed by the reaction of the product with phenylhydrazine, which gave 3,4,5-trimethyl-1-phenylpyrazole.

## 3. Deuteration

Treatment of a solution of 2,4-dimethylbenzodiazepine in benzene with gaseous DCl led to N-deuteration but no C-deuteration (63JA3354). There is an implication here that H/D exchange does not take place at C-3, as happens in 2,3-dihydro-1,4-diazepines, for traces of either the tautomeric



SCHEME 32

form of the base or of the cation should result in some uptake of deuterium at C-3.

#### 4. Bromination

Lack of reactivity at the 3-position toward electrophiles is also evident from the identity of the products obtained by bromination of benzodiazepines.

Monobromination of 2,4-dimethylbenzodiazepine in a mixture of acetic acid and nitromethane provided a deep blue salt, which was designated as 3-bromo-2,4-dimethylbenzodiazepinium bromide (62JPR156). However, an alternative product, which was brown-yellow, was obtained from the reaction of *o*-phenylenediamine with 2-bromo-1,1,3,3-tetraethoxypropane (62JPR156).

The structure of the blue salt was based on its being hydrolyzed to give bromoacetone, but this could equally well be derived from a 2-bromo-methyl-4-methylbenzodiazepinium salt. An authentic sample of the latter salt was later prepared from equimolar amounts of 2,4-dimethylbenzodiazepine and bromine in chloroform [76JCS(P1)2353]. This product was blue, its structure was confirmed by its  $^1\text{H}$  NMR spectrum, and its melting point was similar to that of the earlier so-called 3-bromo derivative. It seems evident that the latter was in fact the 2-bromomethyl compound.

Monohalogenated 2- and 4-methyl groups readily undergo nucleophilic substitution; for example, 2,4-bis(bromomethyl)benzodiazepine gives the 2,4-bis(iodomethyl) analog when treated with sodium iodide in acetone (49HCA1584).

A blue tetrabromo derivative has also been prepared [65JCS3785; 76JCS(P1)2353]. Nuclear magnetic resonance spectra showed that this is the 2,4-bis(dibromomethyl)benzodiazepinium bromide; a corresponding hexabromo derivative was obtained by bromination of 7,8-dibromo-2,4-dimethyldihydrodiazepine [76JCS(P1)2353]. When either of these polybromo derivatives was treated with excess bromine in acetic acid, yellow products were obtained that, from analysis and NMR spectra, appeared to be 3,7,8-tribromo-2,4-bis(tribromomethyl)-3*H*-benzodiazepine. This can be reduced catalytically to give 7,8-dibromo-2,4-bis(dibromomethyl)benzodiazepine [76JCS(P1)2353].

The lack of bromination at the 3-position is in stark contrast to the extremely ready bromination at the 6-position (analogous to the 3-position in benzodiazepines) of 2,3-dihydro-1,4-diazepines or -diazepinium salts [93AHC(56)1]. The latter compounds possess, respectively, vinamidine or vinamidinium systems, which are readily susceptible to halogenation at the central carbon atom. In contrast to these dihydrodiazepines, 1,5-benzodi-



azepines exist largely as diimines with methylene groups at C-3, which will be much less reactive toward electrophiles. It is possible that undetected small amounts of the conjugated tautomer could be present in solution, but, if so, the 3-position in this tautomer must be markedly less reactive than the corresponding site in the dihydrodiazepines; were it to have similar reactivity some 3-bromo product would almost certainly be formed. Lower reactivity at the 3-position of the conjugated tautomer could be expected because of conjugative interaction between the vinamidine system and the benzene ring, leading to a lowering of the electronegativity of the 3-position. In the diimine form the methylene and methyl groups are both activated by the vicinal imine groups, but bromination appears to take place preferentially at the methyl groups, which are more readily accessible to attack. Attempted bromination of 2,4-diphenylbenzodiazepine in the presence of copper salts gave a product in which the bromine present formed part of an anion rather than being attached to the organic cation (73JINC1457).

### 5. Nitration

Attempts to nitrate 2,4-dimethylbenzodiazepine, either by copper(II) nitrate or urea nitrate (65JCS3785) or by a mixture of nitric and sulfuric acids (70CHE1059, 70KGS1133) led only to the formation of tars, but in the latter case 4-nitro-1,2-di(acetylamino)benzene was isolated, which could have arisen from a combination of nitration in the benzene ring and hydrolysis of the 7-membered ring; hydrolysis would be assisted by the presence of the nitro group (see Section VI).

### 6. Nitrosation

When 2,4-dimethylbenzodiazepine was treated with sodium nitrite in acetic acid, the major products were 2-methylbenzimidazole and 2-acetyl-3-methylquinoxaline; the latter product could arise by initial nitrosation at C-3 to form a 3-hydroxyimino derivative that underwent rearrangement and hydrolysis (59JCS1132). Also isolated in low yield was a compound that, on spectroscopic evidence, was assigned the structure 1-nitroso-2,4-dimethyl-1*H*-benzodiazepine.

### 7. Diazo Coupling

2,4-Diphenylbenzodiazepine reacted with *p*-nitrobenzenediazonium chloride to give a yellow crystalline product that, from IR spectra, could be the *p*-nitrophenylhydrazone of 2,4-diphenylbenzodiazepine-3-one (59JCS

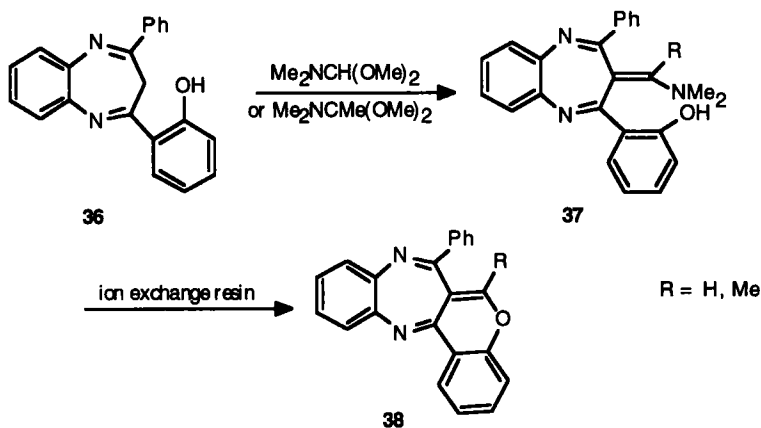
1132). No diazo coupling took place between less-reactive benzenediazonium chloride and 2,4-disubstituted (methyl or phenyl) benzodiazepines (81JHC1341).

### E. CONDENSATION REACTIONS

Benzaldehyde takes part in condensation reactions with the methyl groups of 2,4-dimethylbenzodiazepine in the presence of base; with aqueous alkali a mixture of mono- and di-condensation products are formed, with sodium ethoxide in ethanol only the di-condensation product, 2,4-distyrylbenzodiazepine, is formed (59JCS1132; 66MI1). The resultant products are yellow and with mineral acids give, respectively, purple (2-methyl-4-styryl) and green (2,4-distyryl) salts. When the distyryl compound is treated with aqueous alkali, it is partially hydrolyzed to the 2-methyl-4-styryl derivative (59JCS1132).

In contrast, piperonaldehyde condenses at the 3-position to give 2,4-dimethyl-3-piperonylidenebenzodiazepine together with a small amount of a dipiperonylidene derivative in which a further condensation reaction has taken place at one of the methyl groups. Hydrolysis of the 2,4-dimethyl-3-piperonylidene derivative with hot acid produces 2-methylbenzimidazole, 2-piperonylidenebenzimidazole, and piperonylideneacetone (59JCS 1132). 2,4-Diphenylbenzodiazepine did not condense with benzaldehyde (70BCJ809).

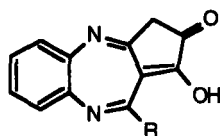
The benzodiazepine (36) reacted with the dimethylacetals of *N,N*-dimethylformamide or *N,N*-dimethylacetamide to give the 3-(aminometh-



SCHEME 33

ylene) derivatives (**37**), which underwent ring closure to (**38**) on treatment with an ion exchange resin in toluene (73S148; 77AP964) (Scheme 33).

Diethyl oxalate condensed with either 2,4-dimethyl- or 2-methyl-4-phenyl-benzodiazepines at both the 2- and 3-positions to give the products (**39**) (60CB2752; 66CB2709; 66MI1).



**39** R = Me or Ph

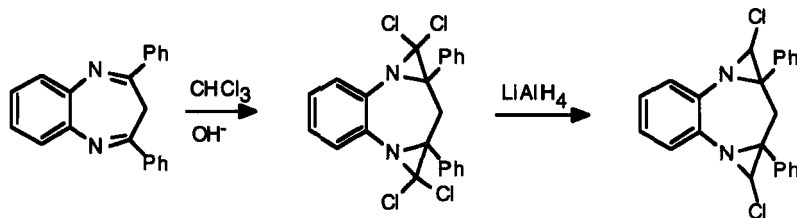
## F. CYCLOADDITION REACTIONS

The imine groups of benzodiazepines can participate in cycloaddition reactions to form both mono- and bis-adducts. In this way 3-, 4-, 5-, and 6-membered rings have been annelated to the diazepine rings. Much of this work has been motivated by the observation that a number of annelated benzodiazepines have interesting pharmacological properties (78MI2).

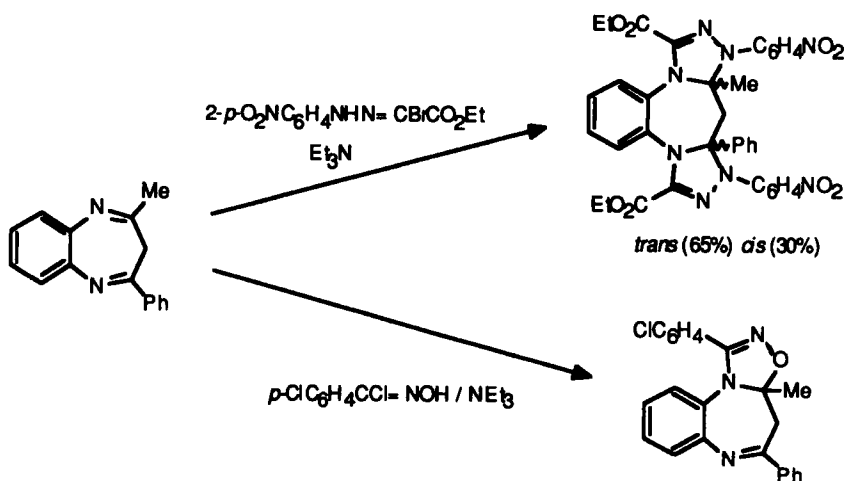
Dichlorocarbene reacts with benzodiazepines to provide bis(chloroaziridino) derivatives, e.g., (87JHC797) (Scheme 34).

Nitrileimines [86S230; 94BSB743; 95AX(C)1352] and nitrile oxides [96AX(C)2281] react to give, respectively, dihydrotriazolo and dihydrooxazolo derivatives, (e.g., Scheme 35). In each of the examples shown the structures of the products have been proved by X-ray crystallography.

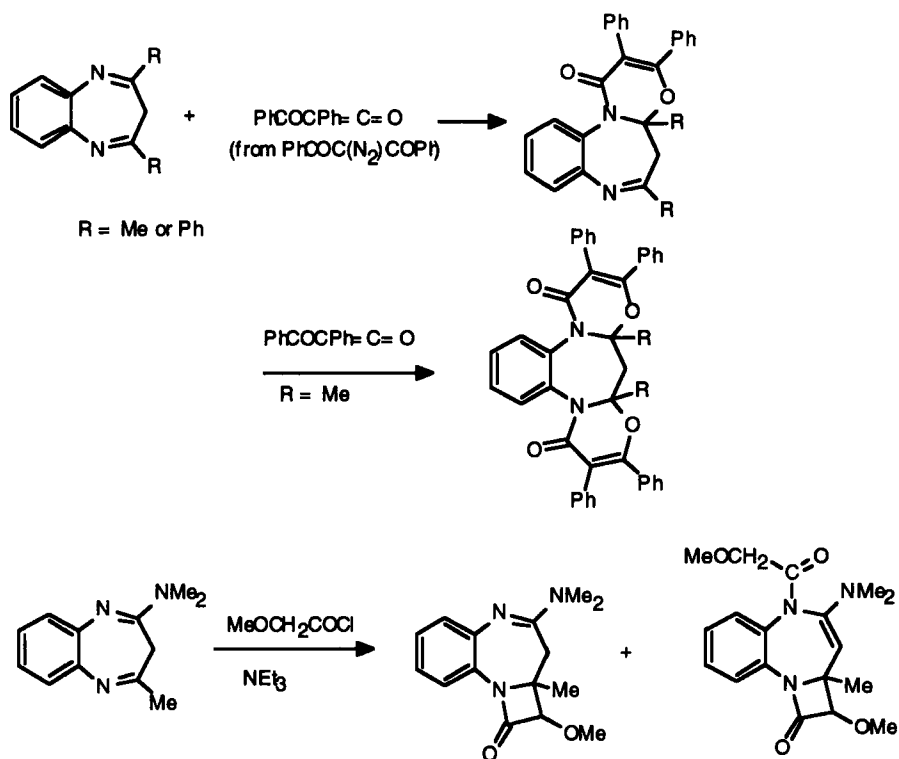
Examples are known of ketenes undergoing either  $[4\pi + 2\pi]$  (81JHC1341) or  $[2\pi + 2\pi]$  (83JHC161; 89JHC119) cycloaddition reactions (e.g., Scheme 36).



SCHEME 34



SCHEME 35



SCHEME 36

## VII. 2(4)-Thio- and 2(4)-Aminobenzodiazepinium Salts

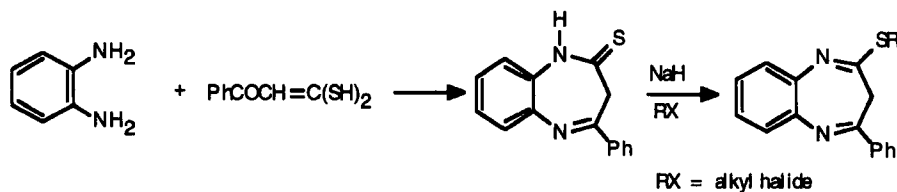
There has been interest in 2(4)-amino- and 2(4)-thio-benzodiazepines because a number of them show physiological and pharmacological activity (see also Section I). Thus, some 2-amino derivatives can behave as tranquilizers, 2-amino-4-thio derivatives show a variety of activity, some as anticonvulsants, others as stimulants, and certain 2-thio derivatives have antibacterial properties.

### A. PREPARATION OF 2-THIOBENZODIAZEPINES

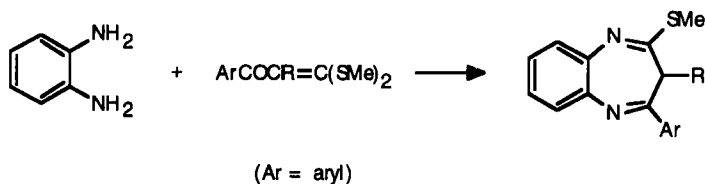
The first preparation of a 2-thiobenzodiazepine involved initial formation of a 2-thione, which was then alkylated (73JHC875) (Scheme 37). The vast majority of 2-thio derivatives have been made in the same fashion, via a thione (75FES248, 75FES727; 75JHC825; 78FES885; 78JMC952; 79FES62; 80FES997; 80H7; 83JHC161). Use of 2-chloroethyldiethylamine as the alkyl halide provided a method for making 2-aminoethylthio derivatives and their quaternary ammonium salts (73JHC875; 75FES248; 75JHC825; 78FES885). The dimercaptoenone can be made by reaction of acetophenone with carbon disulfide (78JMC952). Alternatively the 2-thione has been obtained by thiolation of the corresponding benzodiazepinone (79FES62; 80FES997).

A 2-acetylthiobenzodiazepine is obtained by treating the thione with acetic anhydride (75JHC825). Other variants are the use of dithietane instead of a dimercaptoenone and of diazomethane to convert the thione into a methylthio group (76T483).

Benzoylketene dithioacetals reacted with *o*-phenylenediamine to give 2-aryl-4-thiobenzodiazepines directly, but did not react with mono-*N*-substituted *o*-phenylenediamines (80H7; 92S1273) (Scheme 38). *N*-alkyl-*o*-phenylenediamines reacted with a dimercaptoenone to give a mixture of two isomeric thiones. One of these isomers was treated with sodium hydride followed by 2-chloroethyldiethylamine to provide a 2-(2'-



SCHEME 37



SCHEME 38

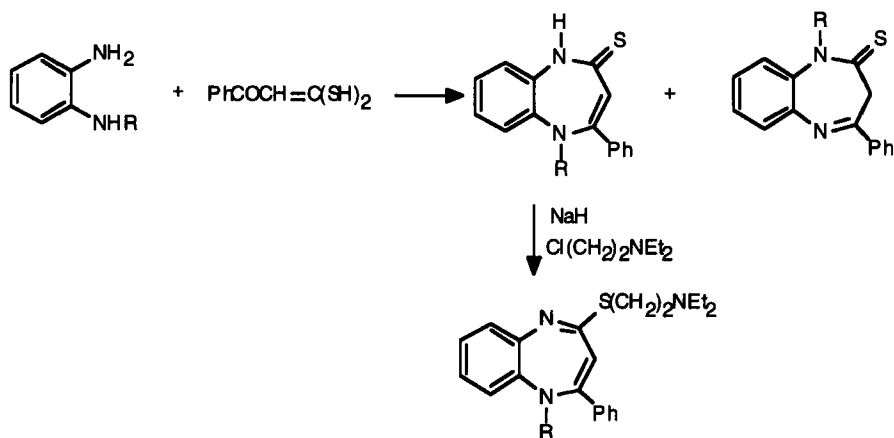
aminoalkylthio)-4-phenylbenzodiazepine (75JHC825; 88JHC305) (Scheme 39).

A totally different approach to the synthesis of 2-thiobenzodiazepines involved the reaction of *o*-phenylenediamine with a trisalkylthiocyclopropenium salt (89T3217) (Scheme 40). The resultant conjugated benzodiazepine changed to a diimine structure when it was purified.

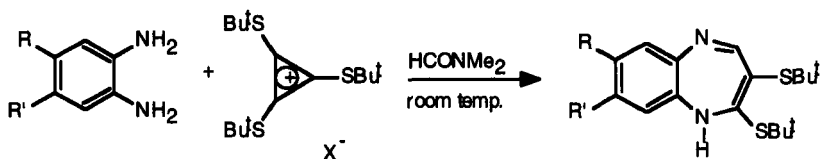
## B. REACTIONS OF 2-THIOBENZODIAZEPINES

Mass spectral studies on 2-methylthio-4-phenylbenzodiazepine, which IR, NMR, and electronic spectra show to exist in the diimine form in solution, suggest that in the gas phase there is a tautomeric equilibrium between the diimine and conjugated forms (90KGS396).

Aqueous acid hydrolyzes the alkylthio group and forms a benzodiazepin-2-one (73JHC875). Oxidation by hydrogen peroxide brings about a similar conversion (80H7). Treatment of *N*-substituted 4-(2'-diethy-



SCHEME 39



SCHEME 40

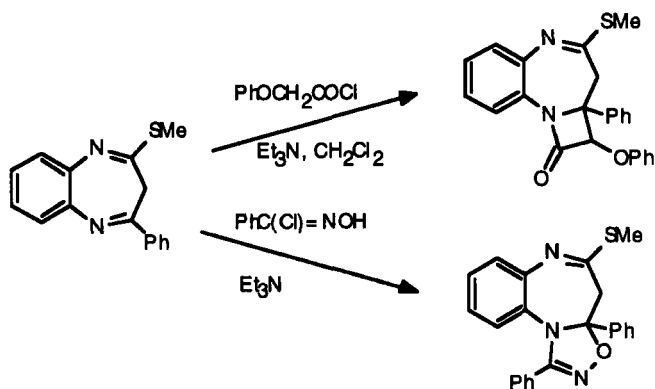
laminoethylthio)benzodiazepines, which must have conjugated structures, with aqueous hydrochloric acid led to the formation of benzimidazoles (75JHC825).

Methylthiobenzodiazepines have been shown to undergo cycloaddition reactions, in a  $[2\pi + 2\pi]$  mode with a ketene (83JHC161) and in a  $[4\pi + 2\pi]$  mode with a nitrile oxide (96JHC1159) (Scheme 41).

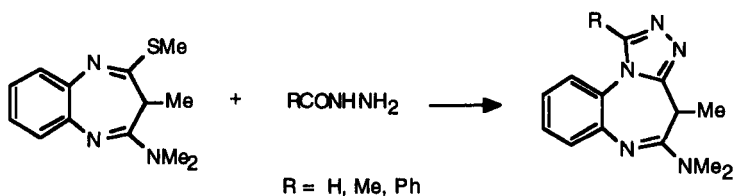
What is in effect a cycloaddition is brought about by combined condensation and substitution reactions when acid hydrazides react with 2-dimethylamino-3-methyl-4-thiobenzodiazepine (90MI1) (Scheme 42). Another method of making a triazolobenzodiazepine, again involving combined substitution and condensation reactions, took place when a 2-thiobenzodiazepine reacted with ethyl carbazate (91JHC365) (Scheme 43).

### C. CONVERSION OF 2-THIOBENZODIAZEPINES INTO 2-AMINOBENZODIAZEPINES

A prime role played by 2-thiobenzodiazepines has been that of convenient precursors for the preparation of a variety of 2-aminobenzodiazepines. The previous paragraph presented examples of the substitution of



SCHEME 41

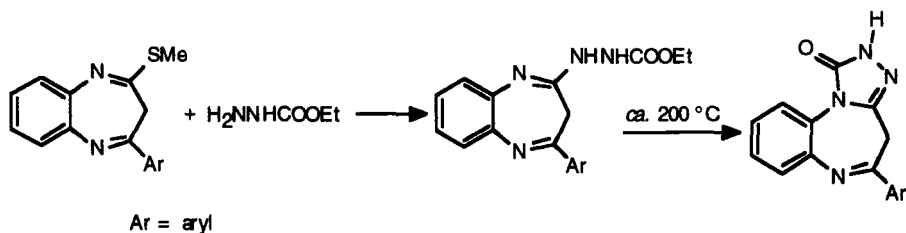


SCHEME 42

thio groups by amino groups. Commonly the methylthio group acts as the leaving group. A good example is provided by the following preparation of a series of 2-*t*-amino-4-arylbenzodiazepines that were required for assay of potential neuroleptic activity (78JMC952) (Scheme 44). Other 2-amino-4-aryl derivatives have been prepared in the same way (80H7), and primary amines as well as secondary amines have been used to substitute the thio group (80FES181). Both 1-unsubstituted (79FES62) and 1-phenyl-2,4-diaminobenzodiazepines (80FES997) have also been prepared in this way, via a 4-amino-2-thione as intermediate, (see, for example, Scheme 45). Many of these aminobenzodiazepines have interesting pharmacological properties.

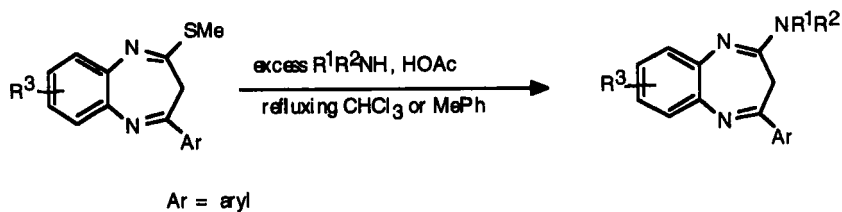
#### D. OTHER METHODS OF PREPARING 2-AMINO-BENZODIAZEPINES

2-Amino-4-arylbenzodiazepines have been made in high yield by reaction of arylalkynylimidate bases with *o*-phenylenediamine. Amidines are formed that, on addition of acid, are converted into benzodiazepinium salts (e.g., Scheme 46) (73JHC399). The method was later simplified by using a tetrafluoroborate salt of the imidate, thereby cutting out the necessity of first liberating the imidate base; this salt reacted with *o*-phenylenediamine in hexamethylphosphoric triamide (HMPA) to provide the benzodiazepinium salt directly without isolation of the intermediate amidine. A key factor is the choice of HMPA, which is known to catalyze nucleophilic addition reactions, as solvent (81JHC1257).

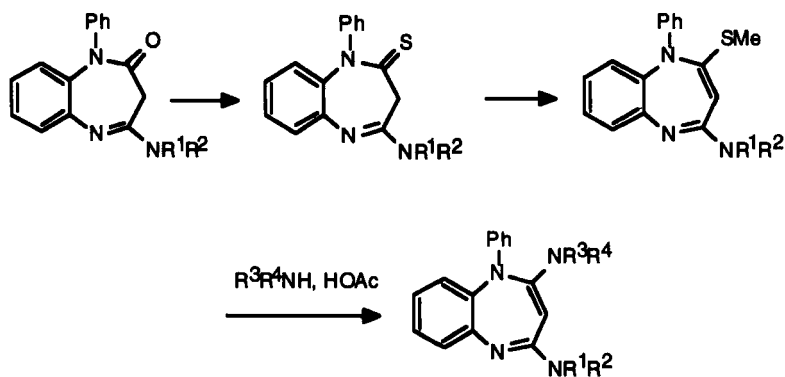


SCHEME 43

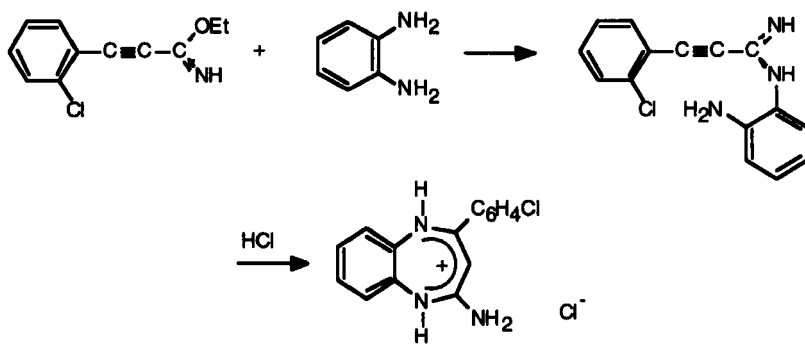




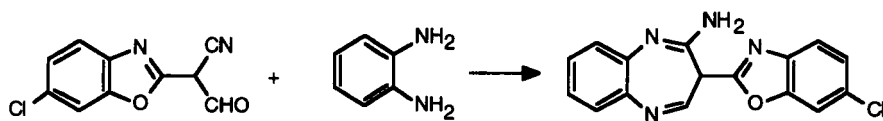
SCHEME 44



SCHEME 45



SCHEME 46



SCHEME 47

The unsubstituted 2-amino group can undergo transamination and be replaced by a di-*N*-substituted amino group by reaction between the benzodiazepinium salt and a secondary amine (81JHC1257). The amino group of 2-aryl-4-phenylaminobenzodiazepine can be methylated, using iodomethane and sodium hydride (89JHC119).

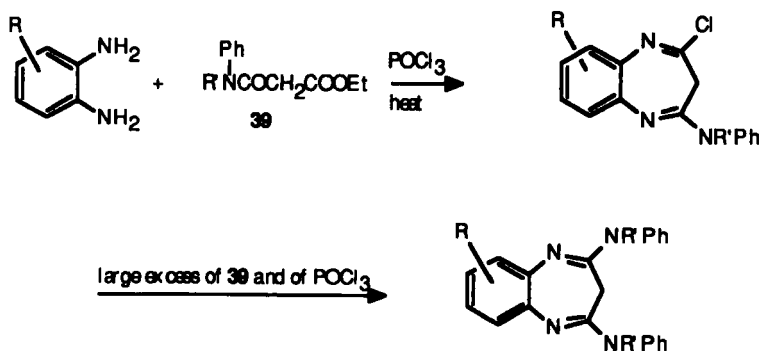
A 2-amino-3-benzoxazolylnitrobenzodiazepine was prepared by reaction of a benzoxazolylnitroacetaldehyde with *o*-phenylenediamine (75IJC304) (Scheme 47).

2,4-Diaminobenzodiazepines have been made starting from *o*-phenylenediamine and *N*-alkyl-*N*-phenylethoxycarbonylacetamides (77FES393) (Scheme 48). If a large excess of phosphorus oxychloride is not used, the product is a 4-aminobenzodiazepine-2-one.

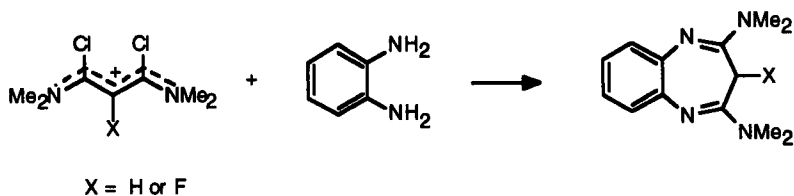
An alternative way of making 2,4-amino derivatives starts from 2,4-dichlorovinamidinium salts [73AG837; 73AG(E)806; 78BSB391] (Scheme 49).

#### E. 2-AMINO-3-CYANOBENZODIAZEPINES AND 2-AMINO-3-ETHOXYCARBONYLBENZODIAZEPINES

2-Amino-3-cyano- and 2-amino-3-ethoxycarbonyl-benzodiazepinium salts are prepared as shown [73JCS(CC)367; 75CPB1391] (Scheme 50). The 3-cyano derivative is very reactive toward nucleophiles at C-4, taking



SCHEME 48

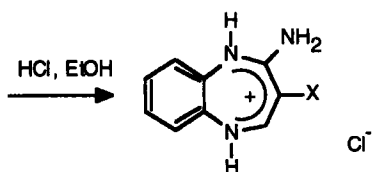
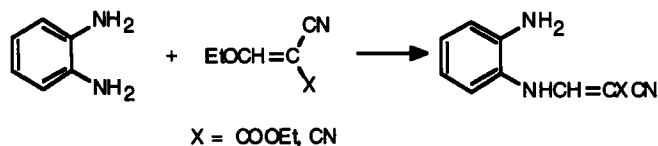


SCHEME 49

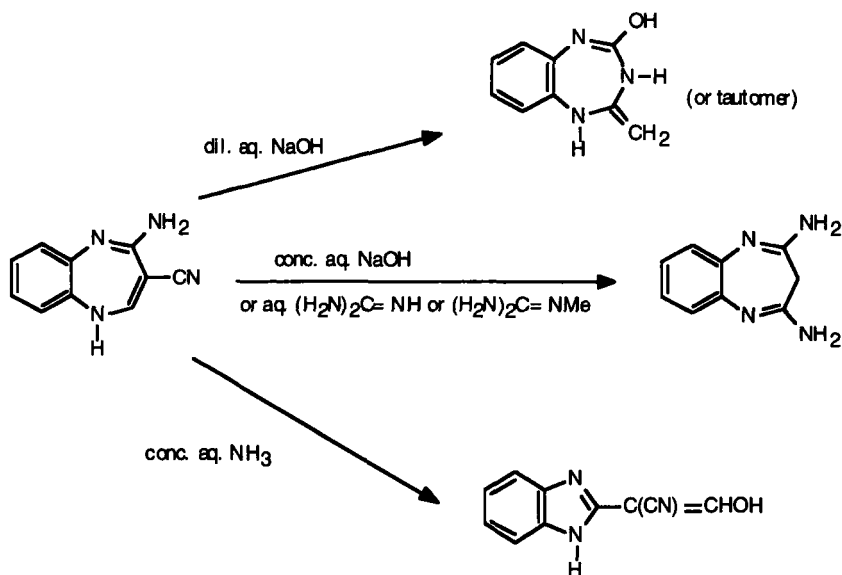
part in reactions that lead to ring-opening involving cleavage of the C-4-N-5 bond. The 3-ester is less reactive (for example, it is converted into the corresponding benzodiazepine base by aqueous alkali), whereas the nitrile undergoes reactions leading to a variety of ring-opened products [73JCS(CC)367; 75CPB1391] (Scheme 51). All of these products are presumed to arise by cleavage of the ring and recyclization to lead to the observed products. In neutral aqueous solution the same benzimidazole is formed, but in acidic solution the product is a 2-(cyanomethyl)benzimidazolium salt (80CPB567).

N-Nucleophiles likewise bring about ring-opening and rearrangement reactions. Thus, primary arylamines lead to the formation of benzimidazoles but primary alkylamines give uncyclized products, for example (86JHC1443; 91JHC485) (Scheme 52). The 3-ethoxycarbonyl analog reacts similarly with aniline.

Hydroxylamine provides a ring-opened product that cyclizes in the presence of acid to form a benzimidazolidine derivative. The latter compound is obtained by reaction of the benzodiazepine with aqueous hydroxylamine hydrochloride (87JHC885; 89JHC277) (Scheme 53). *N*-Methylhydroxy-

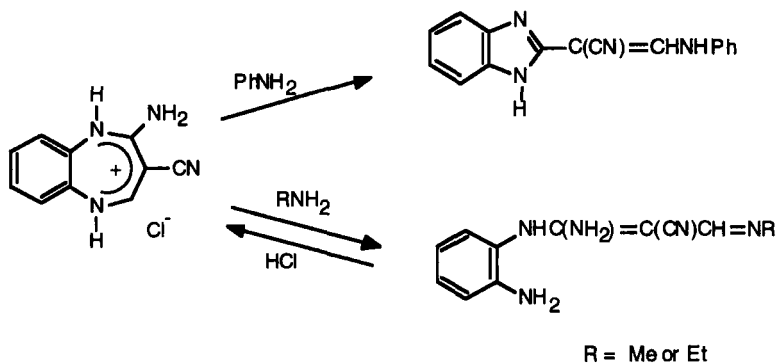


SCHEME 50

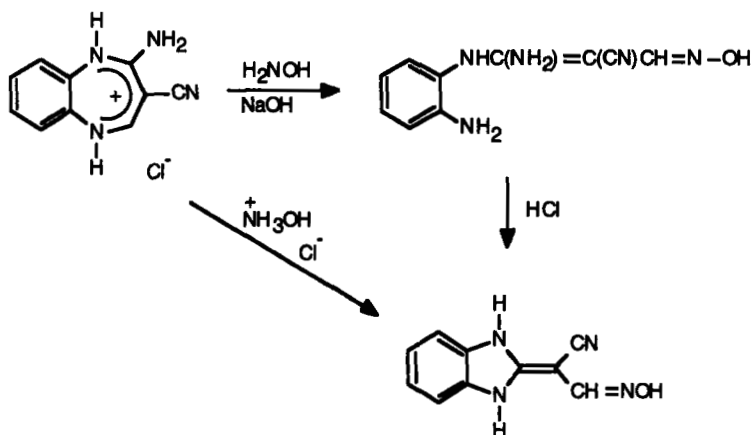


SCHEME 51

amine does not react under similar conditions (87JHC885), but methoxyamine hydrochloride reacts to form a benzimidazole derivative analogous to that obtained from aniline (80CPB567). Hydrazine and its monomethyl and monophenyl derivatives also react to give analogous ring-opened products; these were reconverted into the benzodiazepinium chloride by hydrochloric acid (83CPB2114). In the presence of triethylamine, 2-amino-3-cyanobenzodiazepinium salts reacted with a number of compounds having reactive methylene groups to form open-chain adducts. If 1,8-diazabicy-



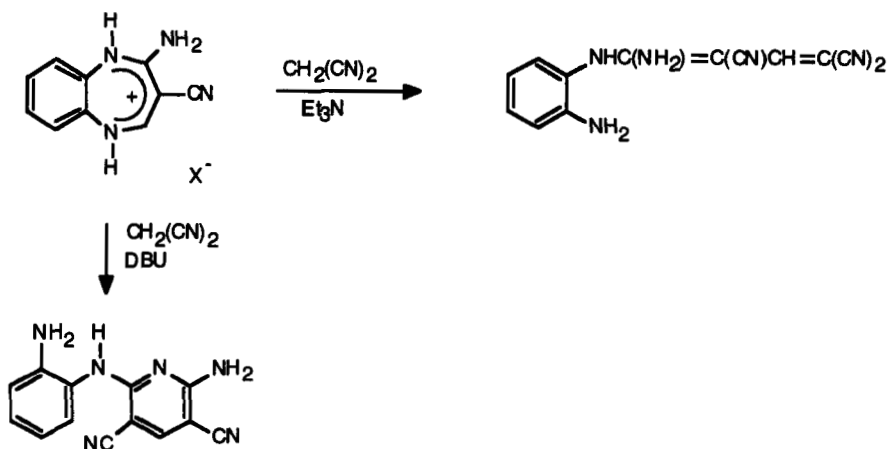
SCHEME 52



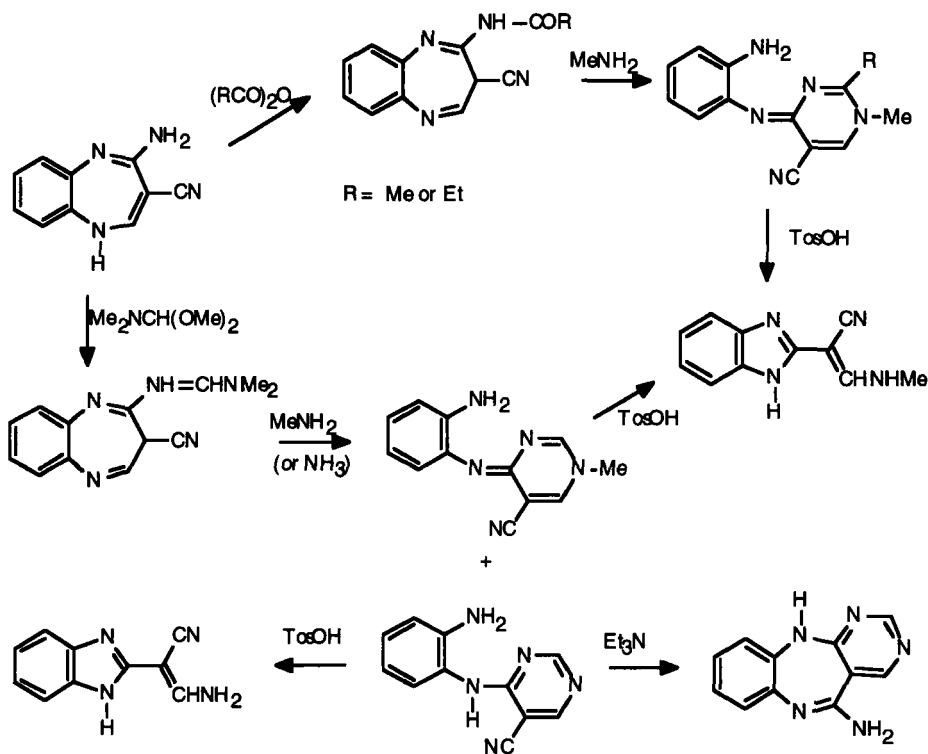
SCHEME 53

clo[5.4.0]undec-7-ene (DBU) is used instead of triethylamine, ring closure ensues to give pyridine derivatives [90JCR(M)0966, 90JCR(S)136] (e.g., Scheme 54). The 3-ethoxycarbonyl analog underwent a similar reaction with malononitrile in the presence of DBU.

The 2-amino group can be acylated, and the resultant products also undergo reactions with amines, leading to opening of the diazepine ring followed by various ring-closure reactions. Examples include the following (87S379) (Scheme 55). Other similar examples involve the 2-ethoxycarbonylamino derivative (86JHC1443; 86S668; 89JHC277) (Scheme 56).



SCHEME 54



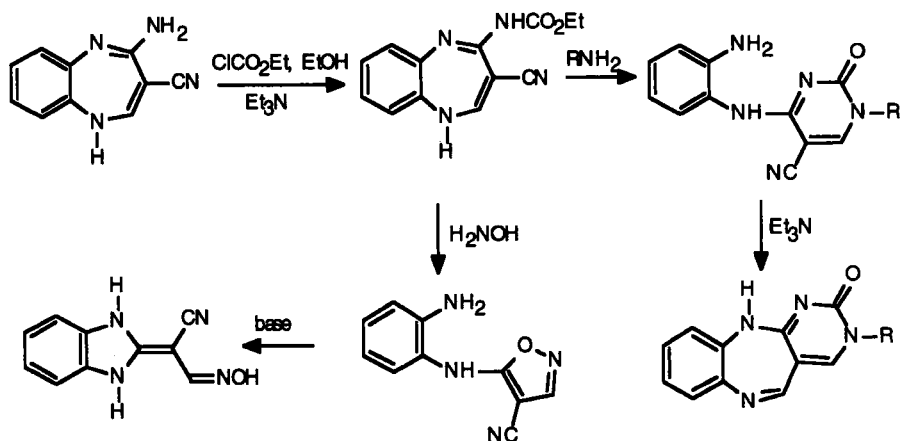
SCHEME 55

The 2-amino group also reacts with alkyl or phenyl isocyanates or phenylisothiocyanates to form 2-ureido derivatives, which cyclize to give tetrahydropyrimidobenzodiazepines (87H1175, 87S379) (Scheme 57).

2-Amino-3-cyanobenzodiazepinium chloride reacted with sodium borohydride to give a mixture of 2,3-dihydro- and 2,3,4,5-tetrahydro-3-cyanobenzodiazepines. It was suggested that deamination, brought about by hydride attack at C-2, preceded reduction (81CPB1165). Similar reduction of the 2-amino-3-ethoxycarbonyl analog provided only 3-ethoxycarbonyl-2,3-dihydrobenzodiazepine.

Oxidation of 2-amino-3-cyanobenzodiazepinium chloride with hydrogen peroxide in the presence of peroxidase as a catalyst gave a benzimidazole (80CPB2325).

It is thus evident that a variety of heterocyclic ring systems can be prepared from 2-amino-3-cyanobenzodiazepines, and in consequence they have attracted some interest as synthetic intermediates. A review of their chemistry (87JHC885) is available.

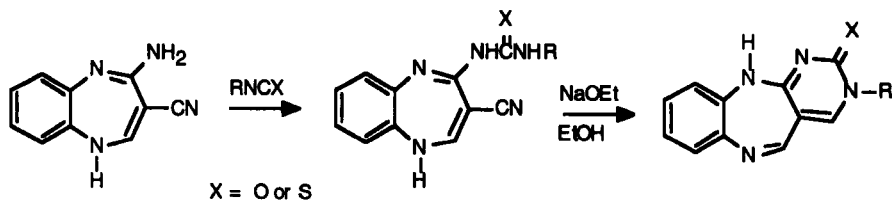


SCHEME 56

### VIII. 3-Oxo- and 3-Methylenebenzodiazepines

At one period there was interest in the preparation of 3-oxobenzodiazepines because they would be heterocyclic analogs of 4,5-benzotropones and hence might be "aromatic" compounds. This incentive was reduced when it became appreciated that benzotropones, and indeed tropones themselves, had no properties that qualified them as aromatic compounds.

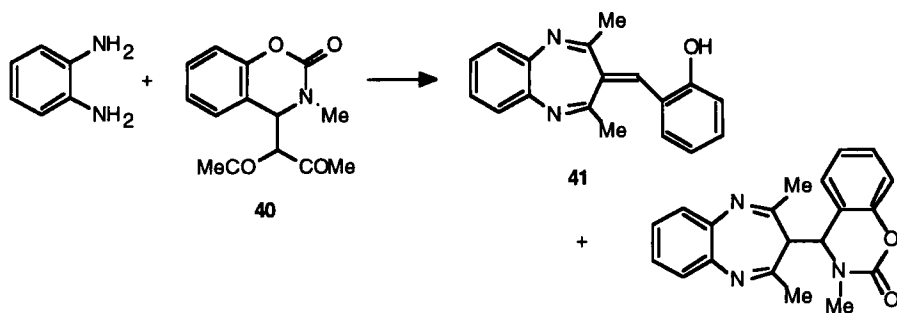
It was not until 1968 that a 3-oxobenzodiazepine was obtained, and then only in 1.4% yield, by oxidation of 2,4-diphenylbenzodiazepine in an atmosphere of oxygen and stimulated by a low-pressure mercury arc. This ketone is unstable and in acid readily loses carbon monoxide to form 2,3-diphenylquinoxaline (68BCJ2543). Further studies of oxidation of benzodiazepines showed that a range of products resulted, and it was suggested that the formation of a number of them could arise via a 3-oxo compound as intermediate, which was then either ring opened hydrolytically or



SCHEME 57

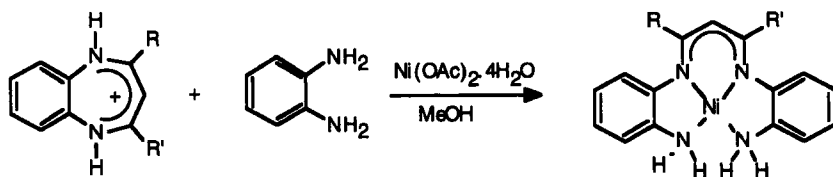
rearranged via a diazanorcaradienone form to provide acylquinoxalines (70BCJ1496) (see Section VI.B).

3-Hydroxyimino-2,4-dimethylbenzodiazepine was prepared by condensation of *o*-phenylenediamine with 3-hydroxyiminopentane-2,4-dione in refluxing benzene [57CI(L)466; 59JCS1132]. Attempts to hydrolyze the hydroxyimino group to a keto group were unsuccessful. Mineral acids caused hydrolytic ring contraction to the oxime of 2-acetyl-3-methylquinoxaline, or under more vigorous conditions to 2-acetyl-3-methylquinoxaline itself [57CI(L)466; 59JCS1132]. Again, an initial isomerization to a diazanorcaradiene form could be involved. Acetic acid or oxalic acid produced 2-methylbenzimidazole, whereas with alkali, among other products, *o*-phenylenediamine, its diacetyl derivative, 2-methylbenzimidazole, and 2-hydroxy-3-methylquinoxaline were formed. When the 3-hydroxyimino-benzodiazepine was heated with dilute acid and acetylacetone, hydrolysis was followed by a recombination of *o*-phenylenediamine with acetylacetone to give a 2,4-dimethylbenzodiazepinium salt [57CI(L)466; 59JCS1132]. Treatment of the 3-hydroxyimino compound with hydroxylamine hydrochloride at room temperature gave the *cis*-oxime of 2-acetyl-3-methylquinoxaline, but when the mixture was warmed the *trans* isomer was formed [69JCS(C)600]. Hydrazine cleaved the molecule to give *o*-phenylenediamine or, in the presence of acid, 2,3-diaminophenazine, and a variety of acyl-, thioacyl-, and aryl-hydrazines gave some *o*-phenylenediamine and reasonable yields of the corresponding hydrazones of 2-acetyl-3-methylquinoxaline. It was suggested that reaction proceeds via partial hydrolysis of the benzodiazepine, but the nature of the by-products shows that some complete hydrolysis must also take place [69JCS(C)600]. A different reaction obtains when the 3-hydroxyiminobenzodiazepine is treated with either semicarbazide, thiosemicarbazide, or *N*-methylthiosemicarbazide, the hydroxyimino group being replaced by the corresponding semicarbazone group (67MI1).



SCHEME 58





SCHEME 59

3-(Diphenylmethylene)benzodiazepine was prepared by reaction of *o*-phenylenediamine with diphenylmethylenemalonaldehide (89CCC2721). Its 2,4-dimethyl analog was prepared similarly from 3-(diphenylmethylene)pentane-2,4-dione (70BCJ809). 3-Benzylidenepentane-2,4-dione reacted with *o*-phenylenediamine in benzene, with or without acetic acid present, to give 2-phenylbenzimidazole, but if piperidine was present some 2,4-dimethylbenzodiazepine was produced, possibly arising from hydrolysis of initially formed 3-benzylidene-2,4-dimethylbenzodiazepine (59JCS 1132). The 3-hydroxybenzylidenebenzodiazepine (**41**) was formed as a yellow crystalline solid, together with a 3*H*-benzodiazepine, in the reaction of the benzoxazinone (**40**) with *o*-phenylenediamine (80JHC519) (Scheme 58).

## IX. Metal Complexes

Benzodiazepinium cations react with many different metal salts to form compounds that are ionic rather than metal-diazepine complexes (71BCJ434; 72BCJ2942; 72JINC1511; 73INCL271; 91JPR327).

Benzodiazepinium salts and their 2-methyl, 2,4-dimethyl, and 2,4-diphenyl derivatives react with *o*-phenylenediamine in the presence of nickel(II) acetate to give a ring-opened metal complex (85IC2276, 85IC2281) (Scheme 59). When *o*-phenylenediamine, acetylacetone, and nickel(II) ions react together to form a 14-membered ring nickel complex, a deep purple color develops in the initial stages of the reaction; it was suggested that a benzodiazepinium cation was an intermediate in the process (80MI1).

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# 1,2,3-Triazolo[*x,y-z*]pyrimidines

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I. Introduction .....	57
II. 1,2,3-Triazolo[1,5- <i>a</i> ]pyrimidines .....	58
III. 1,2,3-Triazolo[1,5- <i>c</i> ]pyrimidines .....	62
IV. 1,2,3-Triazolo[4,5- <i>d</i> ]pyrimidines .....	63
A. 1 <i>H</i> -1,2,3-Triazolo[4,5- <i>d</i> ]pyrimidines .....	63
B. 2 <i>H</i> -1,2,3-Triazolo[4,5- <i>d</i> ]pyrimidines .....	67
C. 3 <i>H</i> -1,2,3-Triazolo[4,5- <i>d</i> ]pyrimidines .....	69
Appendix .....	103
References .....	109

## I. Introduction

Pyrimidines have attracted the attention of organic chemists and biochemists because of their role in biological systems, particularly in nucleic acids, which contain pyrimidines and purines as the main nucleobases. Consequently, the aza analogs of purines, mainly the triazolo and tetrazolo[*x,y-z*]pyrimidines, also are important.

The pyrimidine ring may be condensed with two different triazole rings: the 1,2,3-triazole or the 1,2,4-triazole type. We here review the chemistry, biological activity, and uses of 1,2,3-triazolo[*x,y-z*]pyrimidines, especially compounds of potential chemotherapeutic interest. Work on 1,2,3-triazolo[4,5-*d*]pyrimidines (86AHC117), the aza analogs of purines (63AHC189; 67HC162), and the annulation of a pyrimidine ring to an existing ring (82AHC1) has been reviewed. The triazolo- and tetrazolopyrimidines were covered in the comprehensive heterocyclic chemistry series I (84CHEC847). This chapter reviews the work on the title systems from 1980 to the end of 1995 (*Chemical Abstract* volume **123**) with some additional earlier references.

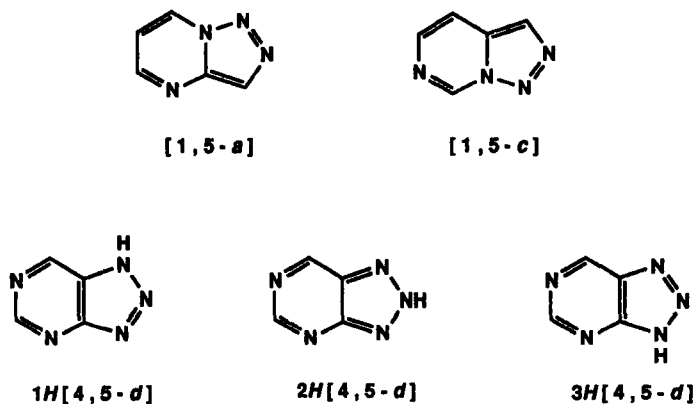
The arrangement of this chapter follows the order of the site of fusion onto the pyrimidine ring, denoted by the letter *z*. The letters *x* and *y* indicate the site of fusion onto the triazole ring. The arrangement of the subdivisions is dependent on the extent of published work.

There are three possible classes of 1,2,3-triazolopyrimidines according to the site of fusion of the two rings. The fusion of the triazole ring may be on one of the carbon–nitrogen bonds of the pyrimidine nucleus to give [1,5-*a*] or [1,5-*c*] rings, which do not display tautomerism. These two ring systems also are named 1,2,3-triazolo[3,4-*a*] and [3,4-*c*]pyrimidines, respectively. On the other hand, fusion on one of the carbon–carbon bonds gives a [4,5-*d*] ring system, which may exist in three tautomeric forms, 1*H*, 2*H*, and 3*H*, according to the location of the proton. However, the N-substituted derivatives are not tautomeric. In addition to the use of the name 1,2,3-triazolo[4,5-*d*]pyrimidine by *Chemical Abstracts*, the 8-azapurine name is used also in the literature. Unfortunately, the numbering with each name is different (86AHC117) (Scheme 1). Both names are used in this chapter.

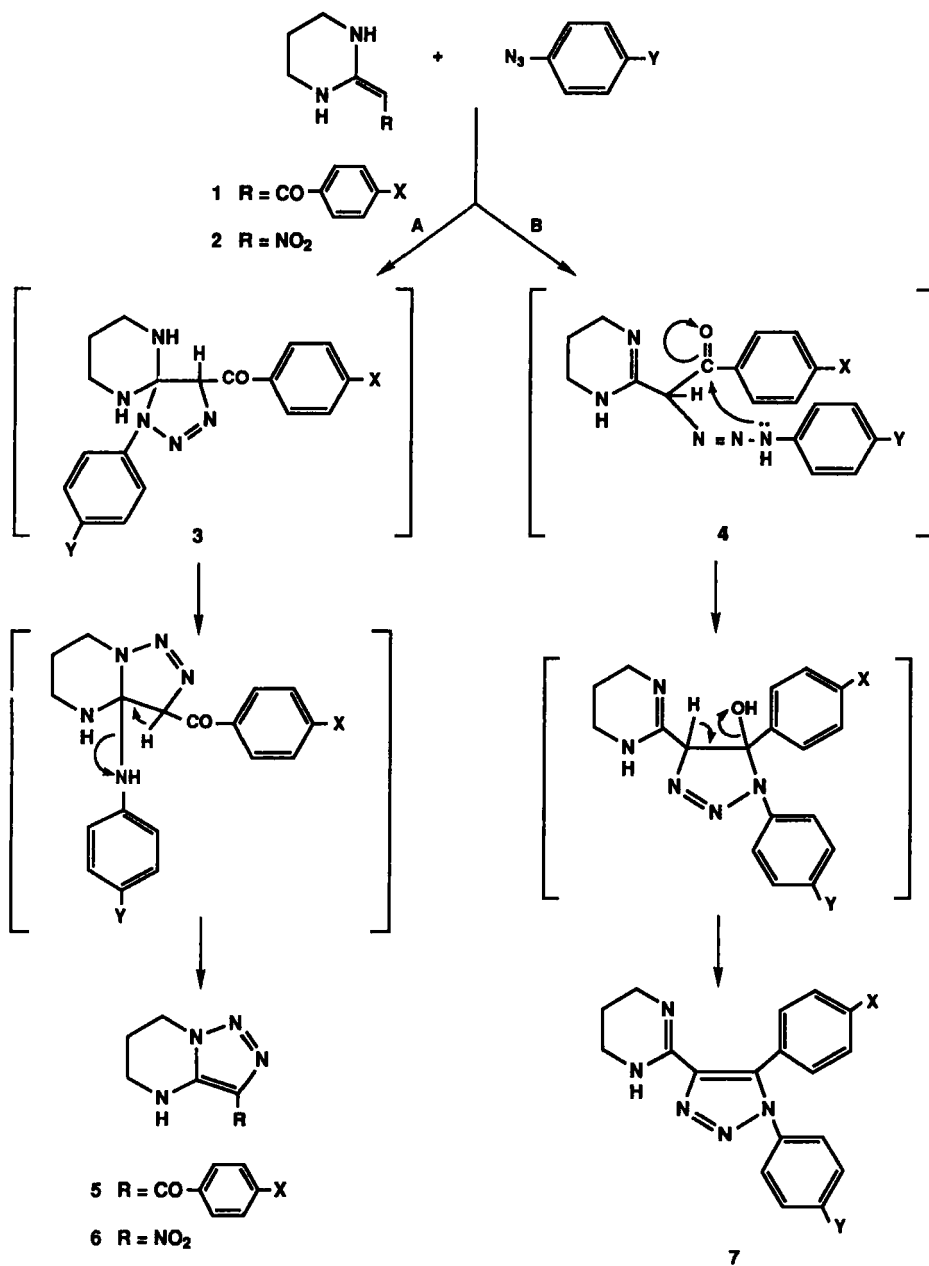
## II. 1,2,3-Triazolo[1,5-*a*]pyrimidines

### 1. Synthesis Based on Pyrimidine Rings

The construction of this ring system may be achieved by building the triazole ring onto a functionalized preformed pyrimidine ring or *vice versa*. Thus, the reaction of hexahydropyrimidines **1** with substituted phenyl azides afforded 3-aryltetrahydrotriazolo[1,5-*a*]pyrimidine **5** in addition to triazoles **7** according to the two competitive reaction pathways **A** and **B**. In route **A**, 1,3-dipolar cycloaddition first took place to form intermediate **3**, which upon Dimroth rearrangement followed by deamination gave the fused heterocycles **5**. In route **B**, cyclic 1,1-enediamines **1** acted as nucleophiles whereby the  $\beta$ -carbon of **1** was only attacked by the terminal nitro-



SCHEME 1

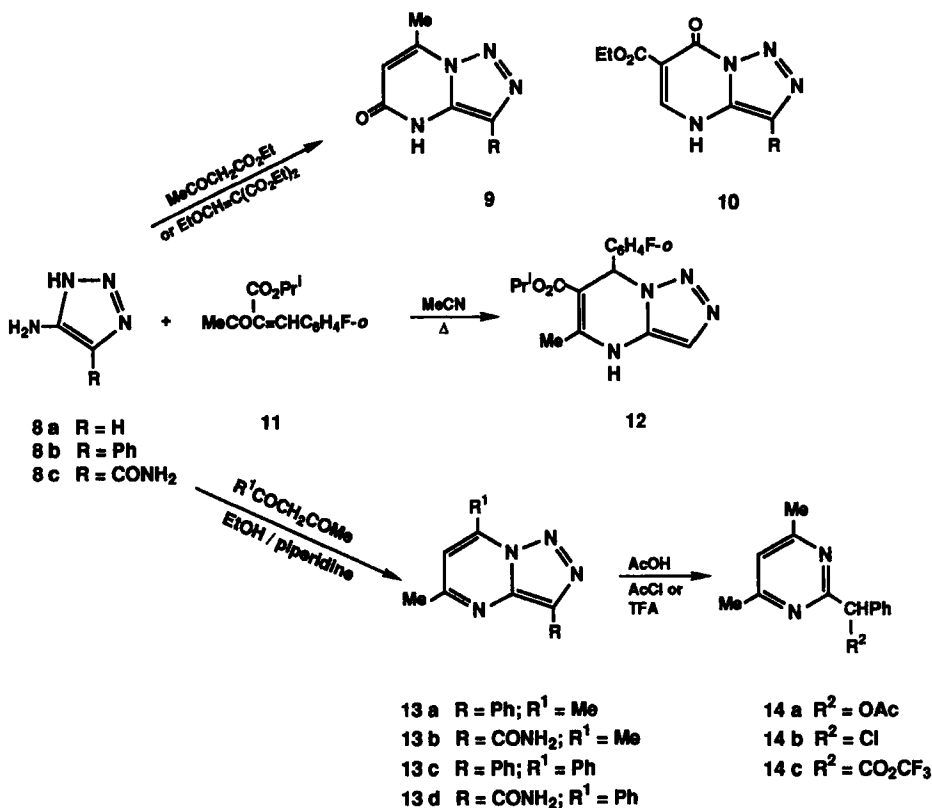


SCHEME 2

gen atom of the azide to form the intermediate **4**. Cyclocondensation of **4** followed by an aromatizing elimination led to the triazoles **7** [92JOC184]. By contrast, reaction of the nitro derivative **2** with *p*-chlorobenzenesulfonyl azide gave 3-nitrotetrahydro-1,2,3-triazolo[1,5-*a*]pyrimidine (**6**) [79JCS(P1) 2361] (Scheme 2).

## 2. Synthesis Based on Triazole Rings

The 5-amino-1,2,3-triazoles **8** react with ethyl acetoacetate and ethyl ethoxymethylenemalonate to give **9** and **10**, respectively [71JCS(C)2156]. Cyclocondensation of the aminotriazole **8a** with isopropyl 2-acetyl-*o*-fluorocinnamate (**11**) gave 4,7-dihydro-1,2,3-triazolo[1,5-*a*]pyrimidine **12** [88JAP(K)63107983]. Condensation of **8b** and **8c** with acetylacetone in ethanolic piperidine afforded triazolol[1,5-*a*]pyrimidine derivatives **13a** and **13b**, respectively. When the reaction with **8b** was carried out in glacial ace-



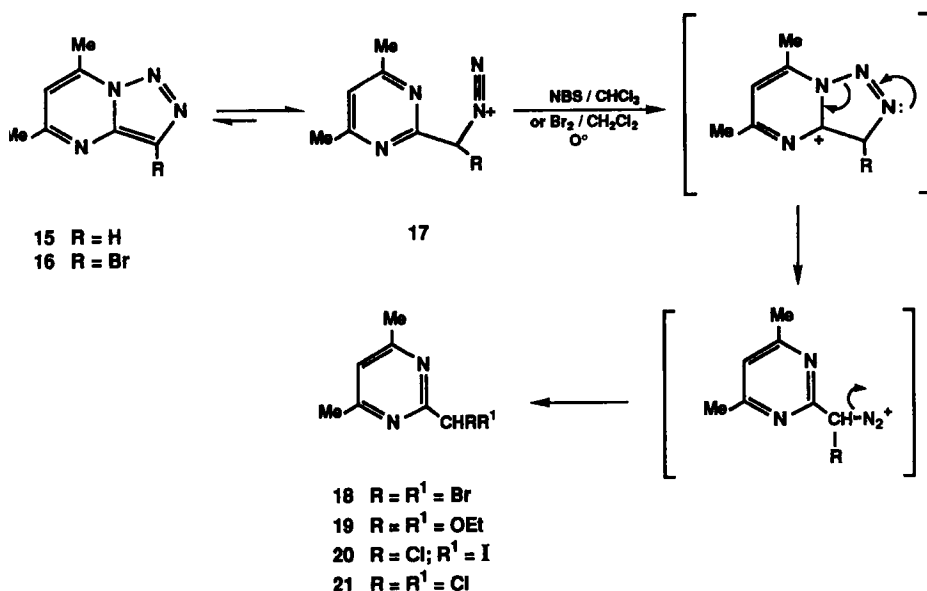
SCHEME 3

tic acid, **13a** accompanied by **14a** was formed. In contrast, heating the 4-substituted triazoles **8b** and **8c** with benzoylacetone or the amide **8c** with acetylacetone in glacial acetic acid gave the triazolopyrimidine derivatives **13c**, **13d**, and **13b**, respectively [71JCS(C) 2156] (Scheme 3).

### 3. Reactivity

Scission of the triazole ring in the triazolopyrimidine **13a** occurred in trifluoroacetic acid or in hot glacial acetic acid alone or in the presence of acetyl chloride, yielding the 2-substituted pyrimidine derivatives **14a-c**. However, **13b-d** were stable to prolonged treatments with acids [71JCS(C)2156].

*N*-bromosuccinimide and **15** gave **18** as the major and **19** as the minor product, not the expected **16** (76JOC385; 83JHC735). Compound **19** resulted from the presence of a trace of ethanol and was not formed when freshly dried chloroform was used. Bromine and **15** in methylene chloride gave **18** but in ethanol gave a mixture of five products, including **16**. Reaction of **15** with *N*-chlorosuccinimide gave **21** and with iodine monochloride it gave **20**. Perhaps **15** may be in equilibrium with, or at least may coexist with, the pyrimidinyl-2-diazomethane **17**. The mechanism is consistent with a cationic route involving diazoalkane as an electrophile (see Scheme 4).



SCHEME 4

#### 4. Biological Properties

Compounds **12** caused increases in blood circulation in coronary and kidney vessels and also showed cardiotonic effects [88JAP(K)63107983].

### III. 1,2,3-Triazolo[1,5-c]pyrimidines

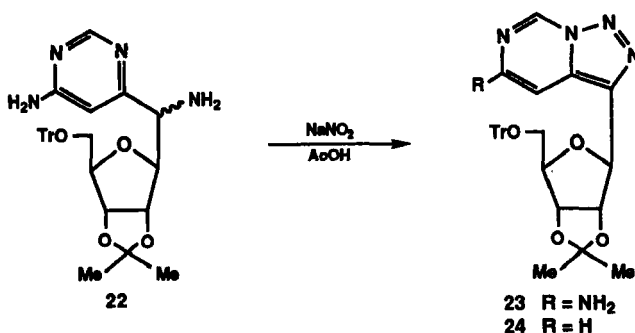
#### 1. Synthesis Based on Pyrimidine Rings

Diazotization of a mixture of diamino derivatives (*R,S*)-**22** afforded the triazolo[1,5-c]pyrimidine **23**. When the reaction time and the proportion of sodium nitrite were increased, a second compound **24**, resulting from a reductive deamination of the amino group [89JCS(P1)2401] was obtained (Scheme 5).

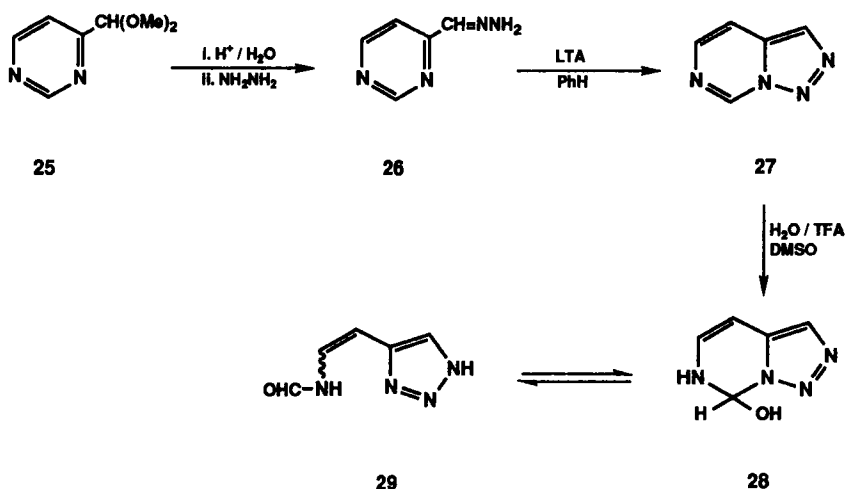
The aldehyde from the hydrolysis of **25** proved to be difficult to isolate but could be converted directly to the hydrazone **26**, whose oxidation with lead tetraacetate gave the 1,2,3-triazolo[1,5-c]pyrimidine **27** (78JHC1041).

#### 2. Reactivity

The covalent hydrate **28** was formed from **27** in the presence of a trace of trifluoroacetic acid or simply on standing. Whereas no evidence of a triazolediazoalkyl-ideneazine valence tautomerism could be found, the presence of **29** as a dominant tautomer was tentatively proposed (78JHC1041) (Scheme 6).



SCHEME 5



SCHEME 6

## IV. 1,2,3-Triazolo[4,5-*d*]pyrimidines

### A. 1*H*-1,2,3-TRIAZOLO[4,5-*d*]PYRIMIDINES

#### 1. Synthesis Based on Triazole Rings

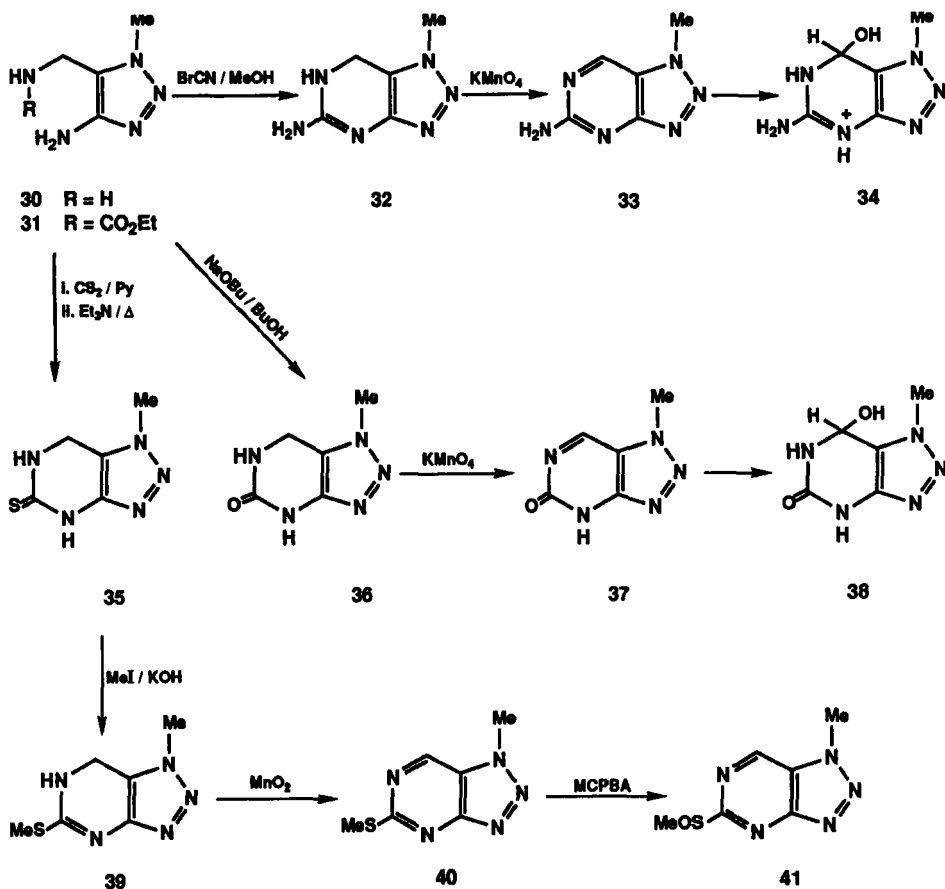
Derivatives are prepared from a suitable functionalized preconstructed 1,2,3-triazole ring such as **30**, which upon cyclocondensation with cyanogen bromide give the amino derivative **32**. The cyclocondensation of **31** with carbon disulfide gave the 1*H*-1,2,3-triazolo[4,5-*d*]pyrimidines **35**, whereas cyclization of **31** in boiling butanolic NaOBu gave **36** [80JCS(P1)2918].

#### 2. Reactivity

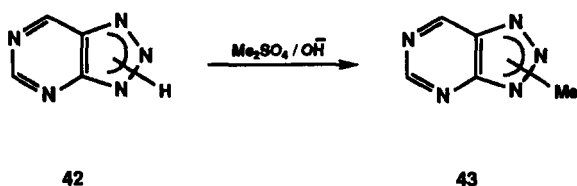
Methylation of **35** afforded the methylthio derivative **39** [81JCS(P1)887]. Dehydrogenation of **32**, **36**, and **39** gave **33**, **37**, and **40**, respectively. Both **33** and **37** have strong covalent hydrating tendencies to form secondary alcohols. Thus, **33** gave cation **34**, whereas **37** formed the neutral species **38**. Oxidation of **40** with *m*-chloroperbenzoic acid gave the sulfoxide derivative **41** [81JCS(P1)887] (Scheme 7).

Methylation of 8-azapurine **42** with dimethyl sulfate in aqueous alkali provided 7-, 8-, and 9-methyl-8-azapurine **43** in approximately equal amounts [69JCS(C)1084] (Scheme 8).



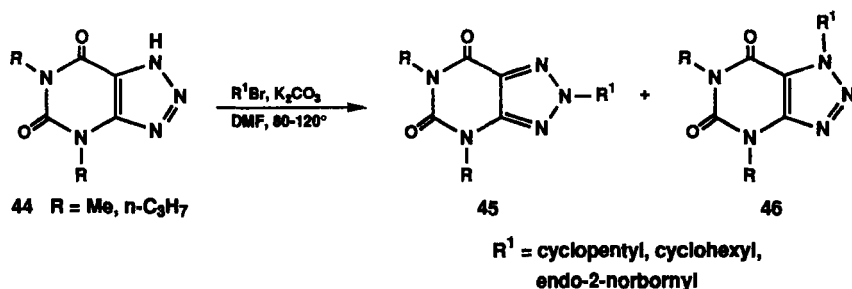


SCHEME 7



SCHEME 8

Alkylation of 8-azaxanthine derivatives **44** with cyclopentyl, cyclohexyl, or *exo*-2-norbornyl bromide in DMF in the presence of K<sub>2</sub>CO<sub>3</sub> gave a mixture of N-8 **45** and N-7 **46** regioisomers (94JMC2970) (Scheme 9).



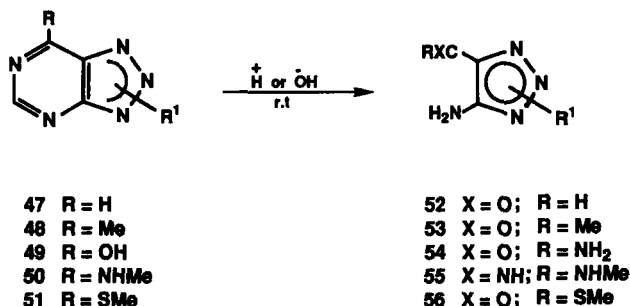
SCHEME 9

Hydrolysis of the *N*-alkyl derivatives of 1,2,3-triazolo[4,5-*d*]pyrimidines **47–51** to give *N*-alkyl-4-aminotriazole derivatives **52–56**, respectively, took place with dilute acid or base at room temperature [57JOC707; 65JOC2488; 69JCS(C)2379; 74JCS(P1)2030; 77JCS(P1)1819] (Scheme 10).

### 3. Physicochemical Data

The electron impact on 8-azaxanthine **57** and its five methyl derivatives **58–62** did not show any exclusively common trend of fragmentation. However, the fragmentation process was characterized by the loss of HNCO or MeNCO followed by consecutive elimination of HCN, CO, and N<sub>2</sub>. Fragmentation of MeNCO was observed only in the case of compounds whose N-1 is replaced by a methyl group [80IJC(B)394].

The crystal and molecular structures of 2-substituted 8-azahypoxanthine derivatives **63** have been determined from X-ray data using MoK $\alpha$  radiation. The propoxy group has a strong intramolecular hydrogen bond to N-1 of the purine, and that in turn led to a planar compound. The 2-propoxyphenyl and *N*-methyl-*N*-isopropylsulfonyl derivatives are present as the *N*-9-*H* tautomers, but the propylsulfonyl compound exists as the

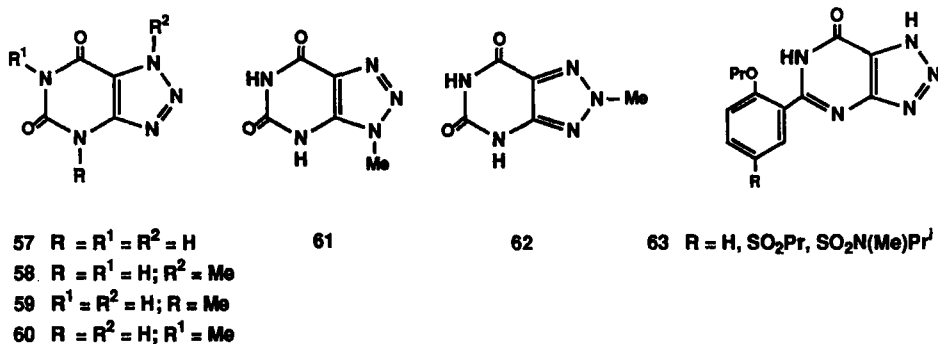


SCHEME 10

*N*-8-H tautomer. CNDO/2 calculations showed that, in all three cases, atom N-9 is very electron rich, whereas the triazole atoms have smaller residual charges (82JA259) (Scheme 11).

#### 4. Biological Properties

A series of 1,3-dimethyl- and 1,3-dipropyl-8-azaxanthines, replaced at the N-8 or N-7 position with substituents that usually increase the affinity of the xanthines for the adenosine receptors was studied in radioligand binding experiments. The replacement of CH by N at the 8-position of both theophylline and caffeine dramatically reduced their affinity; they were inert. The introduction of a methyl group at the 8-position of 8-azatheophylline restored the antagonistic activity at A<sub>2</sub> receptors, and the 8-cycloalkyl substituent increased the affinity for both receptor subtypes. A more favorable effect on affinity was produced by replacing the 7-methyl group in 8-azacaffeine with cycloalkyl groups. 7-Cyclopentyl-1,3-dimethyl-8-azaxanthine was three times more potent than caffeine at A<sub>1</sub> receptors and six times less active at A<sub>2</sub> receptors. By contrast, the 7-cyclohexyl-1,3-dimethyl-8-azaxanthine was more potent than caffeine at A<sub>2</sub> receptors. Replacement of the 1- and 3-methyl groups with propyl in both 7- and 8-substituted 8-azatheophylline increased remarkably the affinity for A<sub>1</sub> receptors. 7-Cyclopentyl-1,3-dipropyl-8-azaxanthine appears to be one of the most potent and selective among the 7-alkyl-substituted xanthines at A<sub>1</sub> receptors. Because the 8-aza analogs of 8-substituted 1,3-dialkylxanthines were less active than the corresponding xanthine derivatives, it was confirmed that the hydrogen atom at the 7-position of xanthines plays an important role in binding to adenosine receptors (94JMC2970).



SCHEME 11

B. 2*H*-1,2,3-TRIAZOLO[4,5-*d*]PYRIMIDINES1. *Synthesis Based on Pyrimidine Rings*

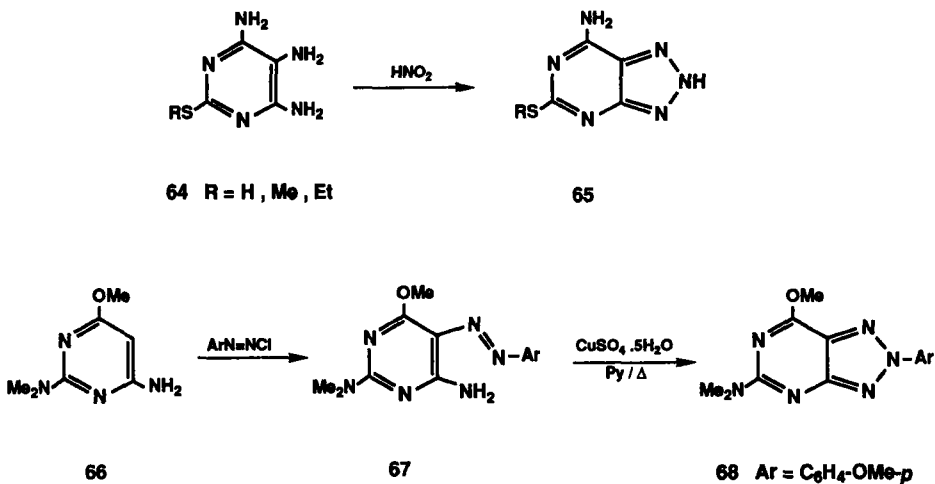
This ring system may be prepared by building the triazole ring onto a pyrimidine ring. Thus, the triazolopyrimidines **65** were prepared by cyclizing the 2-thiolo(alkylthio)-4,5,6-pyrimidine triamines **64** with  $\text{HNO}_2$  (84KFZ325).

The 2-aryl-1,2,3-triazolo[4,5-*d*]pyrimidines **68** were prepared by coupling diazotized *p*-anisidine with 4-amino-2-(dimethylamino)-6-methoxypyrimidine (**66**) to give the azo intermediate **67**, which upon heating in pyridine containing  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  gave **68** (80GEP3001424) (Scheme 12).

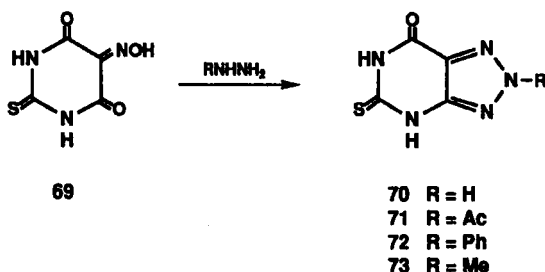
The reaction of 2-thiovioluric acid (**69**) with hydrazine hydrate in boiling ethanol afforded triazolopyrimidine derivative **70**, but in boiling acetic acid yielded *N*-acetyltriazolo[4,5-*d*]pyrimidine derivative **71**. In the same manner, the *N*-phenyl and *N*-methyl-1,2,3-triazolo derivatives **72** and **73** were obtained through the condensation of **69** with phenylhydrazine and with methylhydrazine, respectively (91MI1) (Scheme 13).

2. *Synthesis Based on Triazole Rings*

The pyrimidine ring can also be built onto the triazole ring as shown in the following examples. Azapurine **76** was prepared by ammonolysis of **75**



SCHEME 12



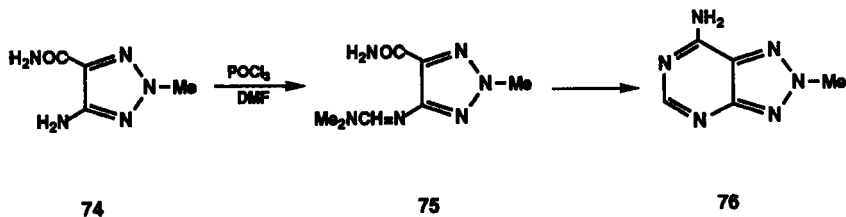
SCHEME 13

obtained from the reaction of 4-amino-2-methyl-1,2,3-triazole-5-carboxamide (**74**) with  $POCl_3/DMF$  (78MI1) (Scheme 14).

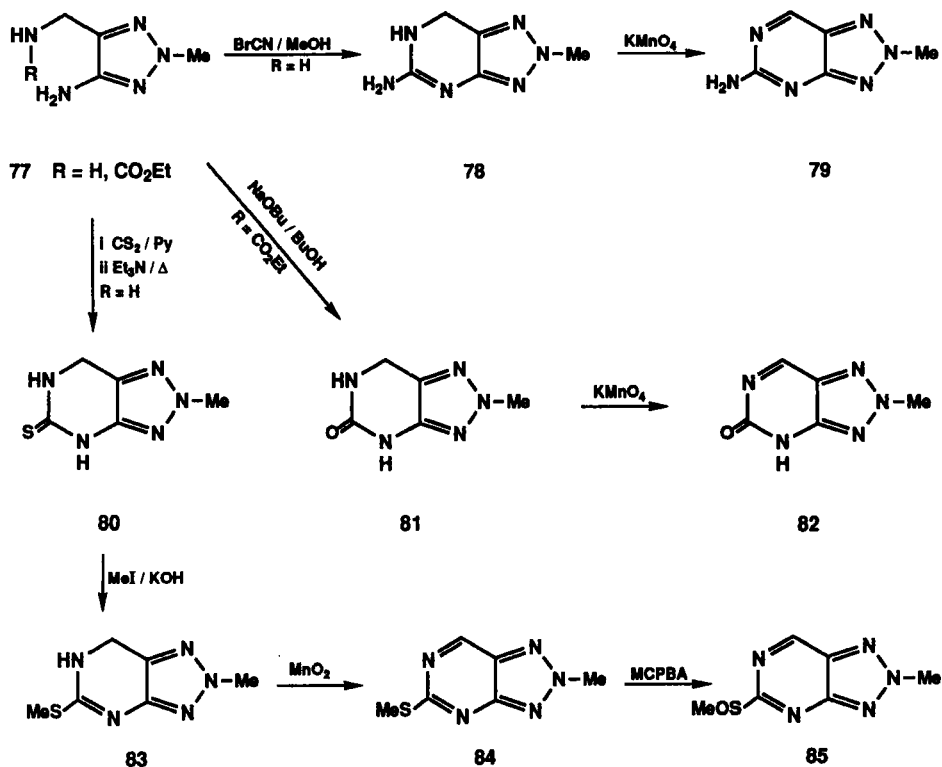
The same strategy that was used for the synthesis of the respective 1-methyl-1,2,3-triazolo[4,5-*d*]pyrimidines was employed for the synthesis of 2-methyltriazolopyrimidine derivatives **78** by cyclocondensation of the triazole **77** with  $BrCN$  [80JCS(P1)2918]. However, cyclization of **77** in boiling butanolic  $NaOBu$  gave **81**, and with carbon disulfide gave the 2-methyl-1,2,3-triazolo[4,5-*d*]pyrimidine **80**.

### 3. Reactivity

Methylation of **80** with iodomethane formed the 2-methylthio derivatives **83** [81JCS(P1)887]. Dehydrogenation of **78** and **81** gave **79** and **82**, respectively. Oxidation of **83** by  $MnO_2$  afforded 8-azapurines **84**, which upon further oxidation with *m*-chloroperbenzoic acid gave the sulfoxide derivative **85**. Both **79** and **82** have strong covalent hydrating tendencies, forming secondary alcohols. The former exhibits this property as the cation, whereas **82** exhibits it as the neutral species (see Scheme 15).



SCHEME 14



SCHEME 15

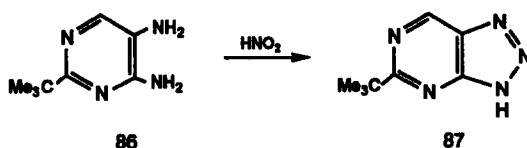
#### 4. Uses and Biological Properties

Compounds **65** have radioactivity protection (84KFZ325), and **68** is useful as a fluorescent whitener for polyester, acetate, acrylic, and polyamide fibers, and for PVC film (80GEP3001424).

### C. 3*H*-1,2,3-Triazolo[4,5-*d*]pyrimidines

#### 1. Synthesis Based on Pyrimidine Rings

This ring can be prepared from diaminopyrimidines by cyclization with nitrous acid. Thus, the triazole ring was readily formed in **86** upon diazotization with nitrous acid to give 5-*t*-butyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**87**) (87JHC705) (Scheme 16).



SCHEME 16

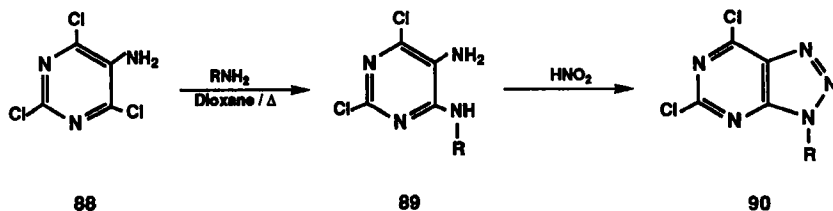
Various approaches were used to form the diamine functionality. Thus, 3-substituted 5,7-dichlorotriazolo-pyrimidines **90** were prepared by condensation of the chloroamines **88** with amines followed by diazotization and cyclization of the resulting diamine **89** to give **90** [84JAP(K)5962593].

The preceding methodology was used for the synthesis of 1,*n*-bis(6-hydroxy-8-aza-9-purinyl)polymethylenes (**93**). Here, reaction of 5-amino-4,6-dichloropyrimidine (**91**) with 1,*n*-diaminopolymethylene gave the amine **92**, whose diazotization gave **93** (91CCC2382) (Schemes 17 and 18).

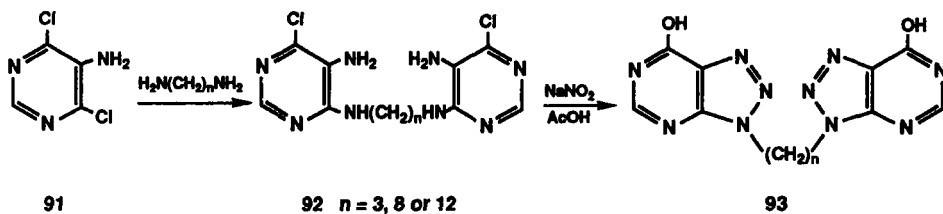
Alternatively, the pyrimidinediamine could be prepared from the nitroamine **94** by hydrogenation followed by diazotization and cyclization to **95** [84JAP(K)5962594].

Similarly, the *N*-amino derivative, 3-amino-5-*t*-butyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**98**) was prepared from **96** first as its benzylidene derivative **97**, followed by the removal of the benzylidene protecting group with dilute hydrochloric acid and DNP (87JHC705). Benzylidene **97** was obtained from the 4-hydrazinopyrimidine derivative **96** in the presence of benzaldehyde followed by cyclization with nitrous acid (87JHC705) (Schemes 19 and 20).

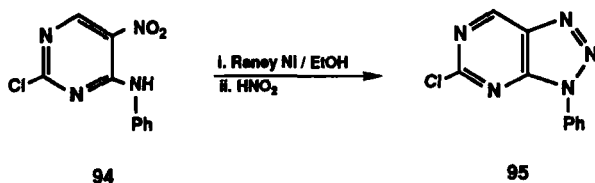
3-Aryl(alkyl)-4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidines (**104**) were prepared by the reaction of *N,N*-dimethylazidochloromethyleniminium chloride (azidophosgeniminium chloride) (**99**), by azido group transfer, with 1,3-dimethyl-4-aminouracils (**100**). This reaction very likely proceeds by the formation of thermally unstable triazine (**101**) intermediate. The latter through N–N bond cleavage gives **103** with the removal of cyanamide **102** as a by-product (87JHC1493). Compound **99** was readily



SCHEME 17



SCHEME 18



SCHEME 19

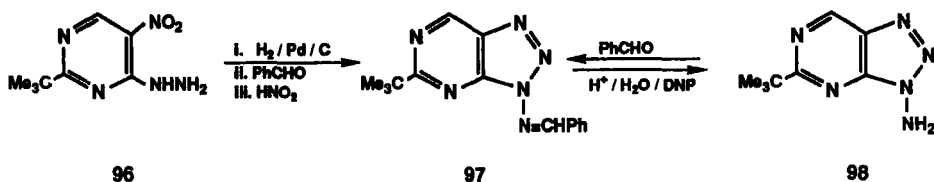
prepared from *N,N*-dimethyldichloromethyleniminium chloride and azido-trimethylsilane (Scheme 21).

## 2. Synthesis Based on Triazole Rings

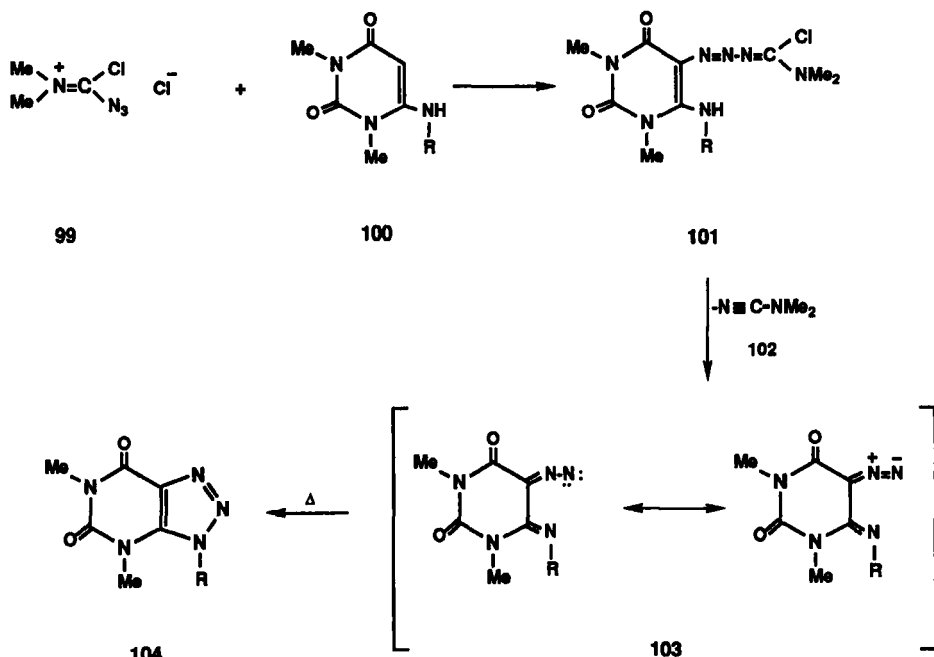
The 5-amino-3-benzyl-1,2,3-triazolo[4,5-*d*]pyrimidine (**106**) was prepared by cyclocondensation of the triazole **105** with BrCN [80JCS(P1) 2918]. Cyclization of **105** by NaOBu in boiling butanol gave **107** (Scheme 22).

The condensation of **108** with tosyl azide gave aminotriazole **109**, which then gave the 3-phenyl-1,2,3-triazolo[4,5-*d*]pyrimidine derivative **110** with  $\text{Me}_2\text{NCH}(\text{OMe})_2$  (90IZV1392). Cyclization of **109** with triethyl orthoformate gave substituted triazole carboxylate **111**, which cyclized with hydrazine to 8-azapurine **112** (90LA819). The cyclized products **113** were obtained by reaction of **109** with excess orthoester, and these in turn were hydrolyzed to the 1-aminohypoxanthine analogs **114**. An attempt to apply these conditions to the nonbenzylated derivative of **109** did not afford cyclized triazolopyrimidine derivatives (85JHC1435). 5-Methylamino-1,2,3-triazole-4-carboxamide and its 1-benzyl derivative **109** were cyclized with HCl and triethyl orthoformate to give 3-methyl-8-azapurin-6(3*H*)-one and its 9-benzyl derivative **115** [81JCS(P1)2344]. Triazolopyrimidines **116** were formed by condensation of **109** and ethyl oxalate. The triazolopyrimidines **117** were prepared by heating the triazole derivative **109** with  $\text{NH}_2\text{CHO}$  (90FA979) (Scheme 23).



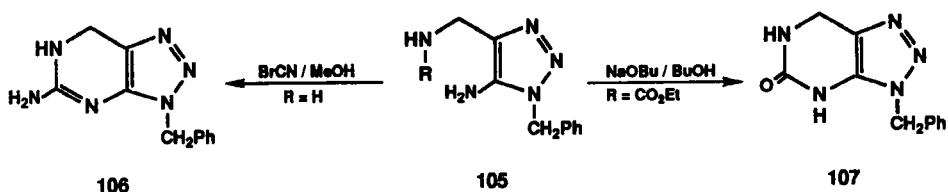


SCHEME 20

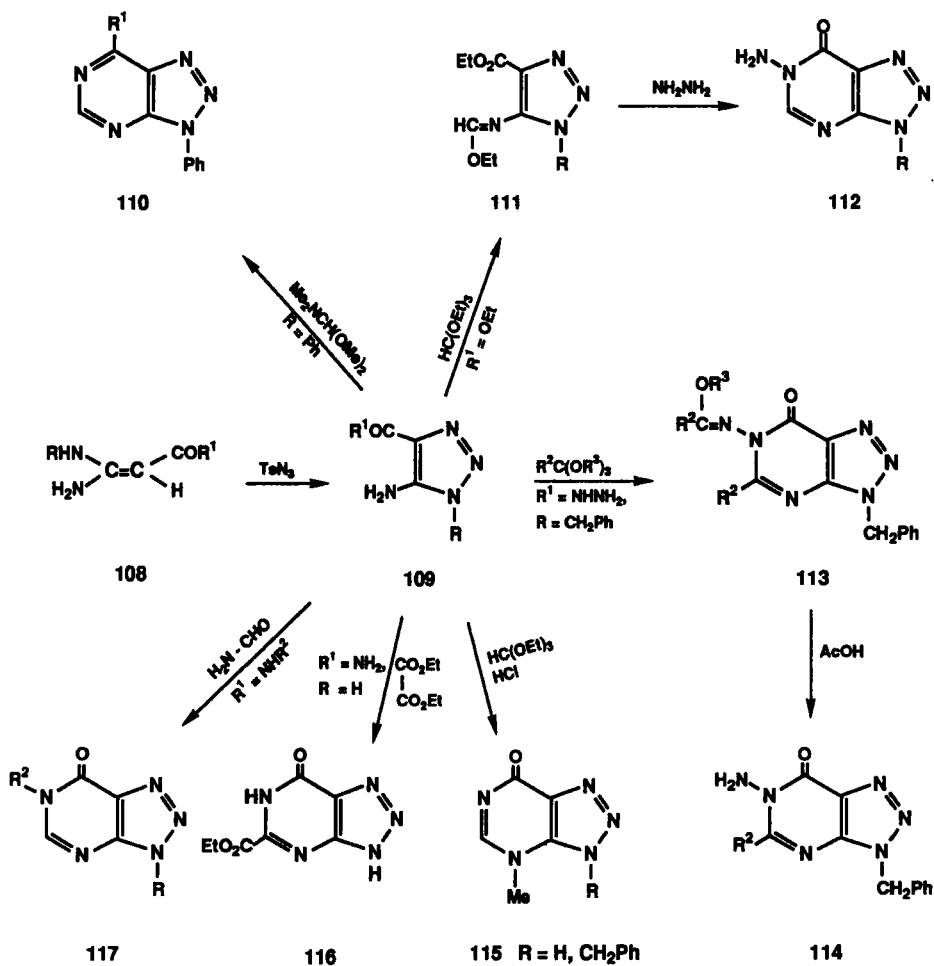


SCHEME 21

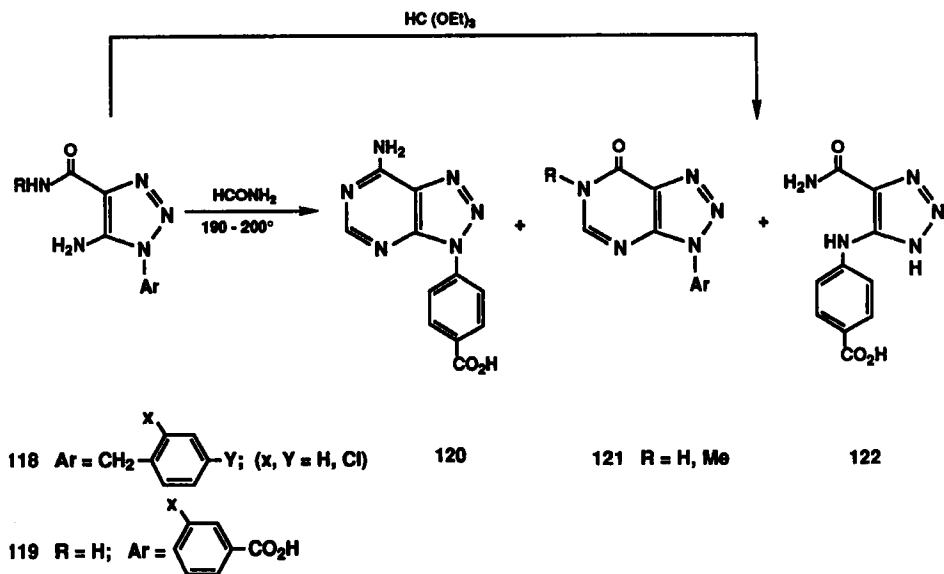
Azapurines were also synthesized by the condensation of 5-amino-1,2,3-triazole carboxamides **118** or **119** with formamide or with formamidinium acetate. When the triazole carried neutral substituents at N-1 such as in **118**, the expected 8-azapurin-6-ones **121** were formed, but when an acidic substituent was present in the same positions as in 4-carboxyphenyltriazolamide **119**, the condensation reaction gave a mixture of 6-amino-8-azapurine **120** together with **121** in addition to a small amount of Dimroth isomer **122**. However, reaction of **119** with triethyl orthoformate gave a mixture of azapurine **121** and an excess of the isomeric triazole **122** (80FES308; 90CZ246) (Scheme 24).



SCHEME 22



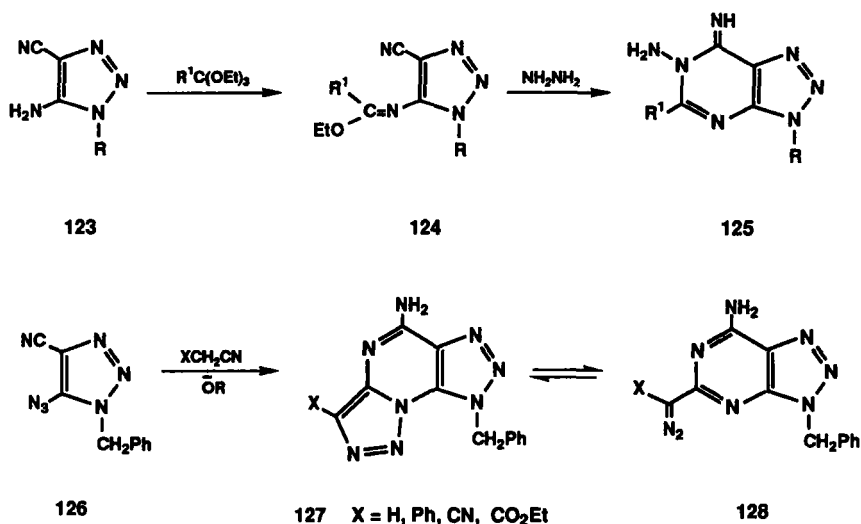
SCHEME 23



SCHEME 24

Condensation of the aminonitrile **123** with orthoesters gave **124**, whose reaction with hydrazine gave triazolopyrimidine derivatives **125** (88 LA1107). The triazolopyrimidines **127** and/or **128** were prepared from 5-azido-1-benzyl-4-cyano-1,2,3-triazole (**126**) and active methylene compounds (phenylacetonitrile, malononitrile, ethyl cyanoacetate, and cyanoacetic acid) in the presence of an alkoxide [85JCS(CC)589]. The equilibrium concentration of the diazo form **128** increases in the following order of the X-substituent: Ph < CN < CO<sub>2</sub>Et < H. The solvent also influences the equilibrium position, stabilizing the diazo form **128** in nonpolar solvents: (CD<sub>3</sub>)<sub>2</sub>SO < CD<sub>3</sub>CN < (CD<sub>3</sub>)<sub>2</sub>CO < CDCl<sub>3</sub>. Upon cooling, the equilibrium shifts toward the ring-closed form **127** [85JCS(CC)589] (Scheme 25).

A one-pot synthesis of 3,5-disubstituted 7-hydroxy-3H-1,2,3-triazolo[4,5-d]pyrimidines (**130**) has been carried out by using benzyl azide, cyanoacetamide, ethyl or methyl esters of the appropriate carboxylic acid, and sodium ethoxide as catalyst. The reaction proceeds via a 5-amino-1-benzyltriazole-4-carboxamide intermediate (85JHC1607). 7-Amino-3H-1,2,3-triazolo[4,5-d]pyrimidines **133** (R<sup>2</sup> = H) were prepared starting from benzyl azide, malononitrile, and an aliphatic or aromatic nitrile, or by reaction of **130** with phosphorus oxychloride followed by amination. Compound **132** was formed in most reactions from two molecules of the 5-amino-4-cyano-1-benzyltriazole intermediate by an intermolecular nucleophilic at-



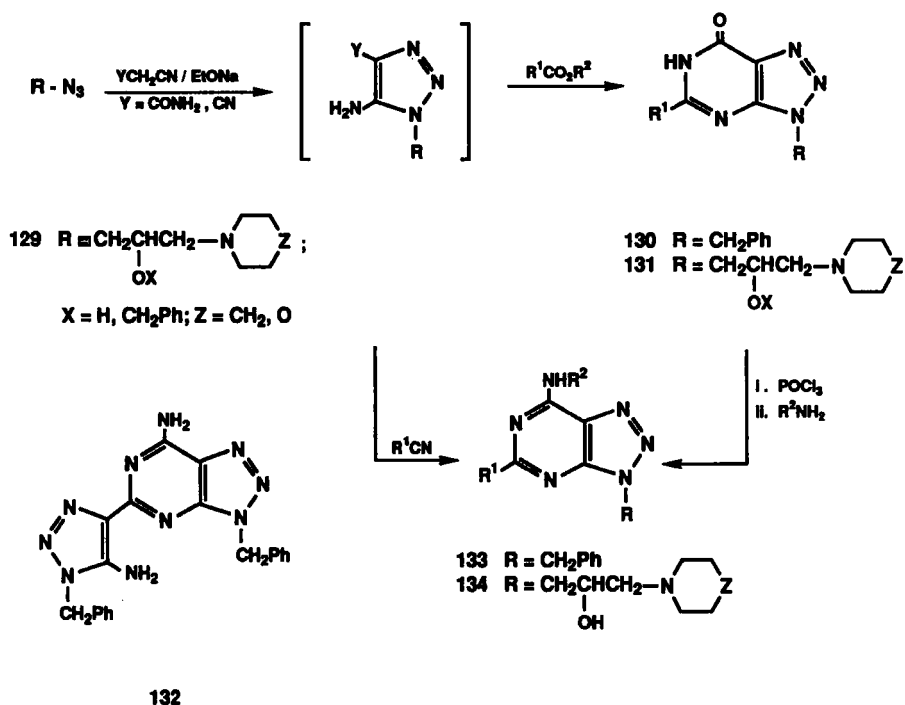
SCHEME 25

tack of an amino group on a cyano group (87JHC997). 8-Azahypoxanthines **131** and 8-azaadenines **134** containing a hydroxyl group bonded to a chiral carbon atom were prepared from a 2-hydroxy-3-aminopropylazide **129**, which was prepared by nucleophilic opening of the oxirane ring of the glycidyl azide with piperidine or morpholine followed by protecting the hydroxyl group (89JHC39) (Scheme 26).

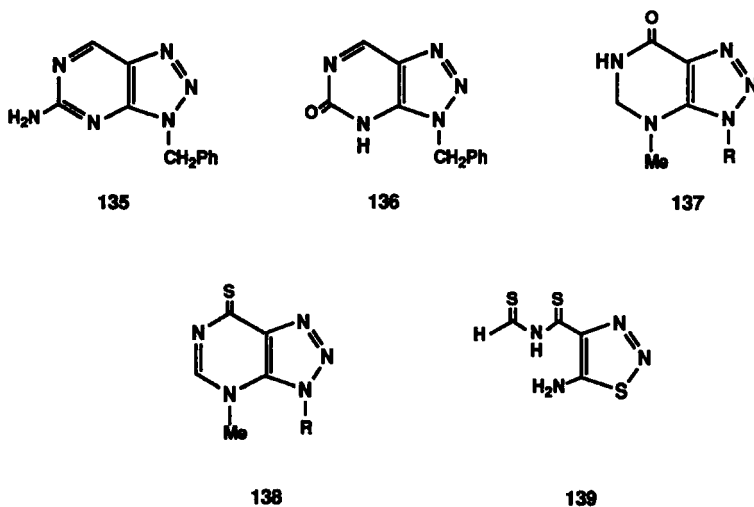
### 3. Reactivity of the Ring and Its Substituents

Dehydrogenation of **106** and **107** gave **135** and **136**, respectively [80JCS(P1)2918]. Catalytic hydrogenation of **115** with Pd-C afforded **137**. Reaction of **115** with P<sub>2</sub>S<sub>5</sub> in pyridine led to the azapurine thione **138** and the by-product **139**. Transalkylation of **116** can be done with an alcohol in the presence of an acid catalyst [81JCS(P1)2344; 90FA979] (Scheme 27).

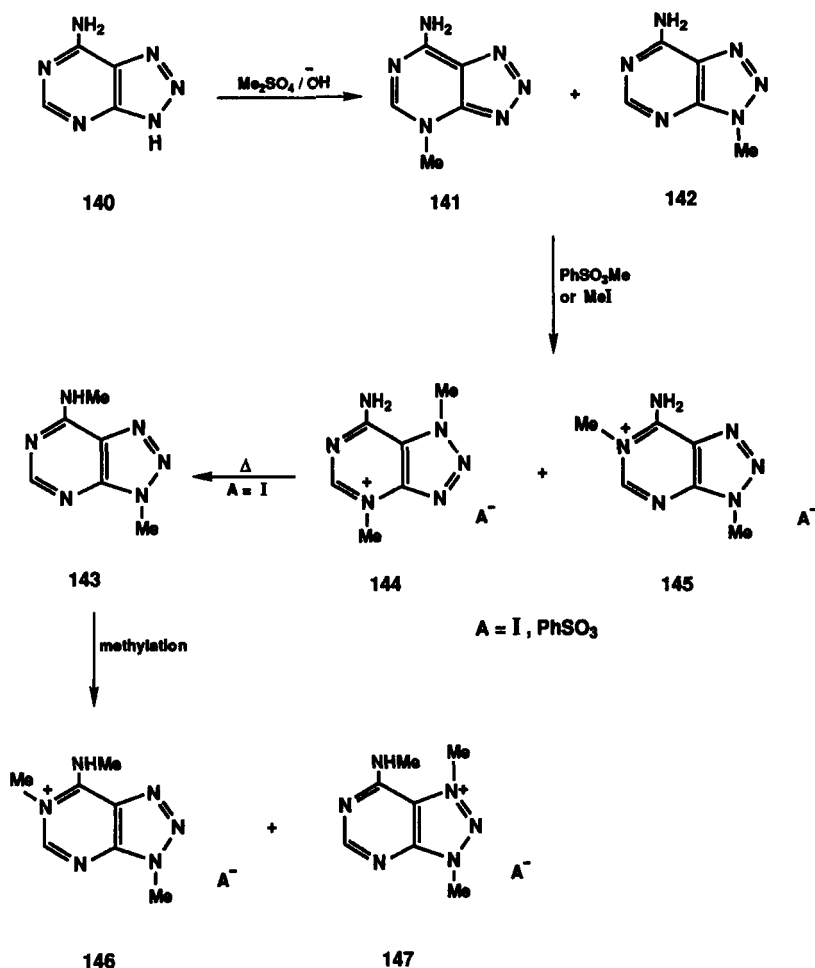
Methylation of 7-amino-1,2,3-triazolo[4,5-*d*]pyrimidine (8-azaadenine) (**140**) with dimethyl sulfate afforded the N-3 and N-9 methylated isomers **141** and **142**, respectively, which upon further methylation with methyl iodide or benzenesulfonic acid methyl ester gave 3,7- and 1,9-dimethyl-8-azaadeninium salts **144** and **145**, respectively. Thermal decomposition of the dimethyl derivatives led to a transmethylation to give 6-methylamino-9-methyl-8-azapurine (**143**), whose methylation afforded 1- and 7-methyl-6-methylamino-9-methyl-8-azapurinium salts **146** and **147** (80ZOR2204) (Scheme 28).



SCHEME 26



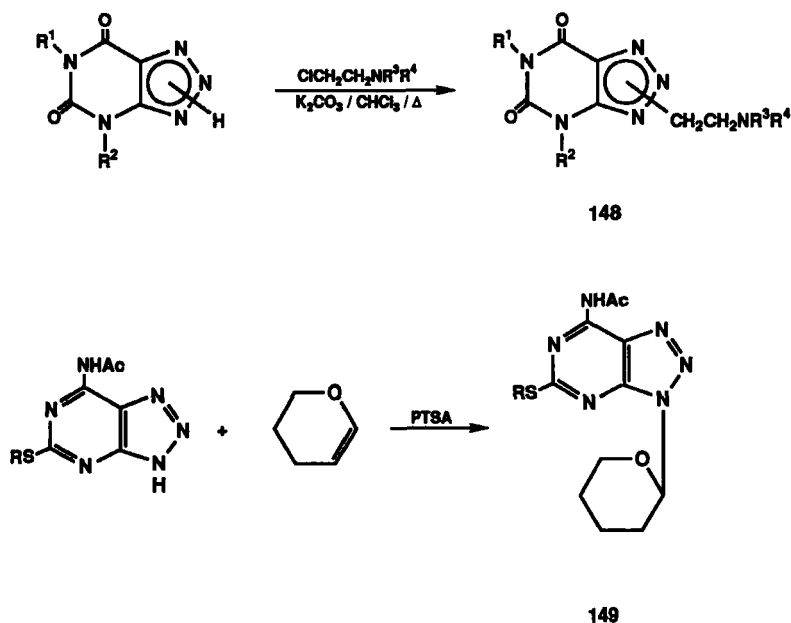
SCHEME 27



SCHEME 28

Reaction of 1,3-dialkyl-8-azaxanthine with 2-dialkylamino- or 2-morpholinoethyl chloride gave the three alkylated triazolopyrimidine derivatives **148** (88EUP272226). Treatment of 6-acetyl-2-alkylthio-8-azaadenines with 3,4-dihydro-2*H*-pyran in the presence of PTSA gave 2-alkylthio-9-tetrahydropyranyl-8-azaadenines (**149**) [84IJC(B)1286] (Scheme 29).

Nucleophilic reagents attack the 7-position of the triazolopyrimidine ring when a leaving group is present. Replacement of the sulfur atom at that position can be achieved after its alkylation. Here, methylation of 3-(3-chlorophenyl)-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dithione (**150**) af-



SCHEME 29

forded the corresponding bismethylated derivative whose reaction with cyclopentylamine gave 3-(3-chlorophenyl)-7-(*N*-cyclopentylamino)-5-methylthio-1,2,3-triazolo[4,5-*d*]pyrimidine (**151**) (91TL3583) (Scheme 30).

Chlorination of triazolopyrimidines **152** with thionyl chloride or phosphorus oxychloride yielded the chloro derivative **153**. Hydrazinolysis of the chlorine atom in **153** gave the hydrazinoazapurine **154** (90CZ246). The substitution reactions can be done also with amines and alkoxides to give **155** and **156**, respectively.

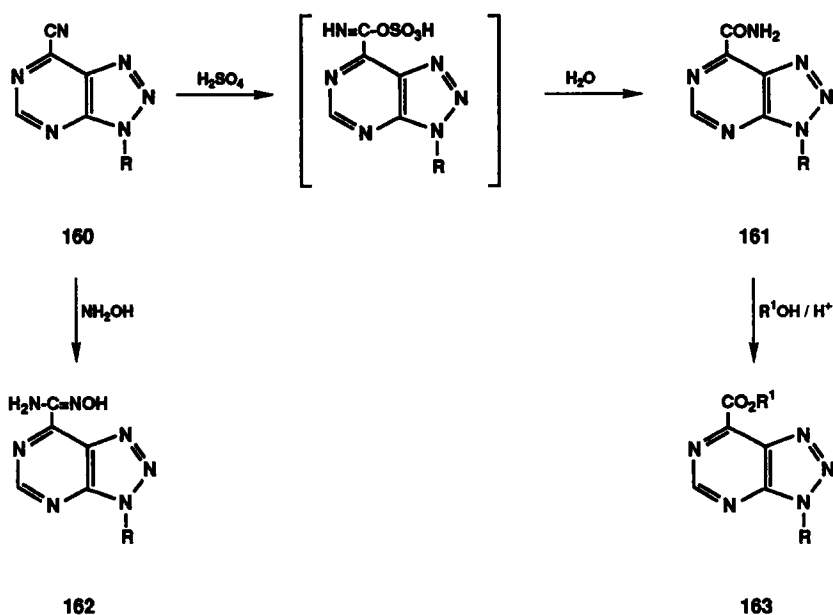
Nucleophilic arylation of **153** to give 7-aryltriazolopyrimidines **157** was achieved by heating with aromatic aldehydes, NaH, and a catalytic amount of 1,3-dimethylbenzimidazolium iodide (DMBI). Treatment of **157** with NaOH/DMSO and then  $K_3[Fe(CN)_6]$  resulted in aryl migration to give **158** (85CPB1395).

A substitution reaction on **153** with carbanions (active methylene compounds in the presence of sodium hydride) gave the 7-substituted derivatives **159**. The oxo group of the latter products enolized to provide a hydrogen bond with the adjacent ring nitrogen (79YZ1031; 80CPB337) (Scheme 31).

The cyano group in **160** underwent addition reactions with sulfuric acid and with hydroxylamine to give the amide **161** and the amidoxime **162**, re-





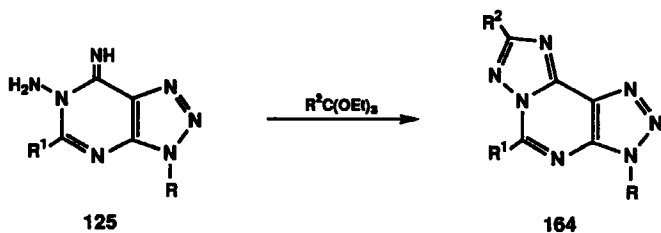


SCHEME 32

spectively. The amide **161** forms the ester **163** with alcohols in the presence of acid (80CPB255) (Scheme 32).

Reaction of the triazolopyrimidines **125** with orthoesters formed the bis-triazolopyrimidine derivatives **164** (88LA1107) (Scheme 33).

The amino group at the 5-position on the 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine ring was converted into a halogen atom by treatment with isopentyl-nitrite in halomethanes. 5-Halotriazolopyrimidines, unsubstituted at the 7-position, reacted with butyllithium to give 7-butyl-6,7-dihydro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines, whereas in the 7-substituted-5-halotriazolopyrimidines a halogen-metal exchange reaction took place and



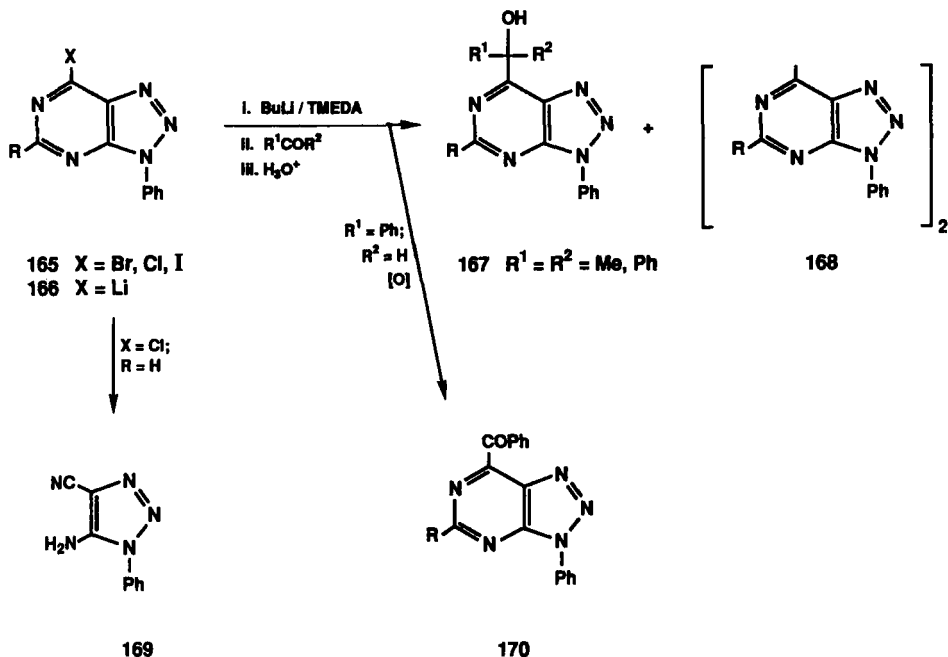
SCHEME 33

the resultant 5-lithio compound reacted with electrophiles to give the 5-substituted triazolopyrimidines (91CPB3037).

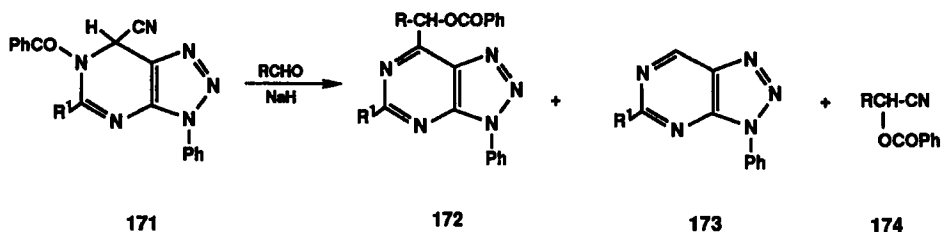
The halogen metal exchange reaction between 7-bromo or 7-iodo-3-phenyltriazolopyrimidine **165** and butyllithium in *N,N,N',N'*-tetramethylethylenediamine afforded the 7-lithio compound **166**, whereas a similar reaction with the 7-chloro derivative **165** ( $R = H$ ) gave the ring-fission product, 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbonitrile **169** (91CPB2793). Reaction of **166** with electrophiles such as benzaldehyde and ketones gave **170** and **167** respectively, together with 7,7'-bis[3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine] **168** (Scheme 34).

Reaction of the triazolopyrimidine **171** with aldehydes in the presence of NaH gave benzoates **172** and the by-products **173** and **174** formed by aromatization (92CPB513) (Scheme 35).

5-(Methylsulfonyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine **176** was prepared by the reaction of **175** with sodium methyl sulfide, followed by oxidation with potassium permanganate in acetic acid. A nucleophilic substitution reaction on **176** with potassium cyanide gave **182**, but the same reaction did not take place on **175**. Treatment of **176** with sodium methoxide



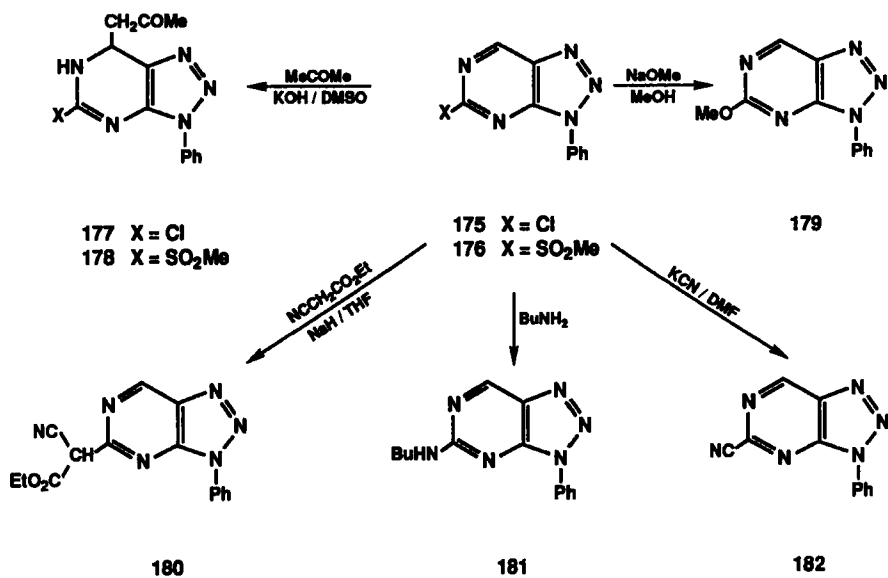
SCHEME 34



SCHEME 35

and butylamine gave **179** and **181**, respectively. Reaction of **175** and **176** with ethyl cyanoacetate in the presence of sodium hydride afforded **180**. Acetone can be added across the C-7-N-6 double bond of **175** and **176** to give **177** and **178**, respectively (89CPB1731) (Scheme 36).

Reaction of the 3-substituted 1,2,3-triazolo[4,5-*d*]pyrimidines (**183**) with one equivalent of a Grignard reagent in THF afforded the dihydro compounds **185** after hydrolysis of the intermediates **184**. Aromatization of **185** by oxidation with potassium ferricyanide (79CPB3176) or with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) (89CPB1731) gave the 3-substituted 7-alkyltriazolopyrimidines **186**. Replacement of the methylsul-



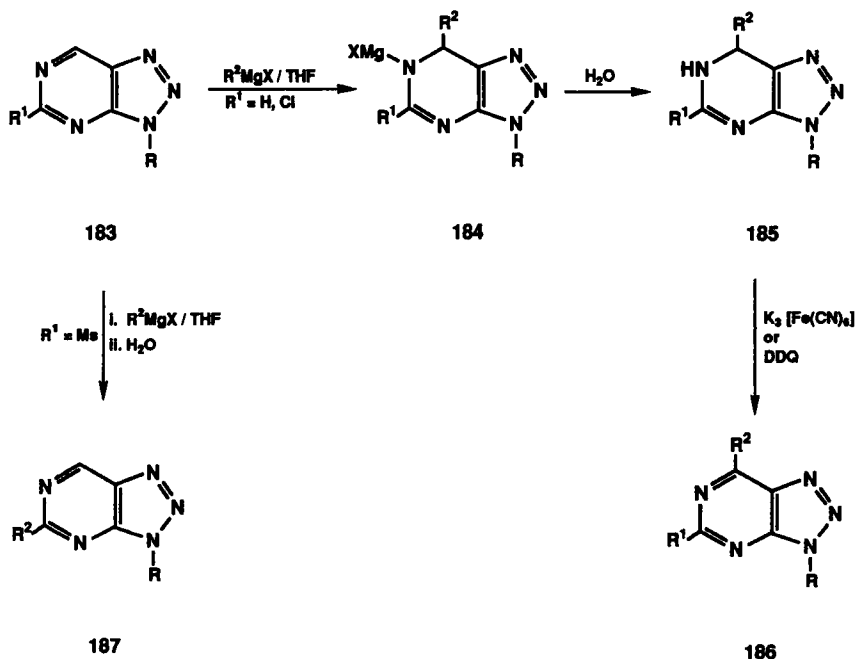
SCHEME 36

fonyl group of **183** with a Grignard reagent gave the 5-alkylated derivative **187** (89CPB1731) (Scheme 37).

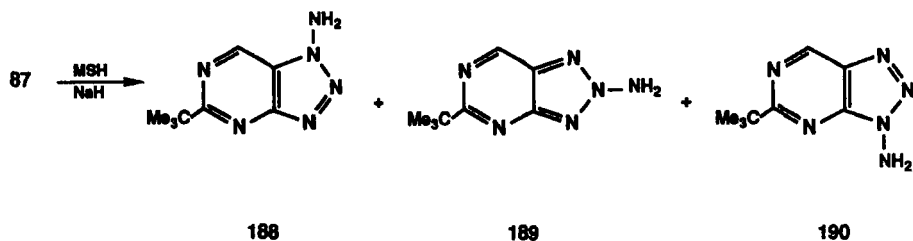
Amination of 5-*t*-butyltriazolopyrimidine **87** with *O*-mesitylsulfonylhydroxylamine (MSH) gave the 1-, 2-, and 3-amino derivatives **188–190**, respectively. The benzylidene derivatives of **188** and **190** were prepared (87JHC705) (Scheme 38).

UV and NMR spectroscopy indicated that the cations of 1,2,3-triazolo[4,5-*d*]pyrimidines undergo reversible addition of water across the 6,7-double bond to form the 6,7-dihydro-7-hydroxy-3*H*-triazolopyrimidine cations. The neutral molecules are essentially anhydrous. The stable anion of 5-hydroxytriazolopyrimidine is anhydrous, but its neutral molecule exists mainly as the covalently hydrated species. Oxidation of **191** with  $\text{H}_2\text{O}_2/\text{H}_2\text{SO}_4$  gave **192**. Reduction of **191** with  $\text{KBH}_4$  gave the 6,7-dihydro derivative **193** [66JCS(B)427; 66JCS(B)433] (Scheme 39).

Complexation of 8-azaadenine with methylmercury(II) hydroxide at different pH values gave the coordinated complexes **194–197**. Their structures have been established by X-ray analysis (86ICA181) (Scheme 40).



SCHEME 37



SCHEME 38

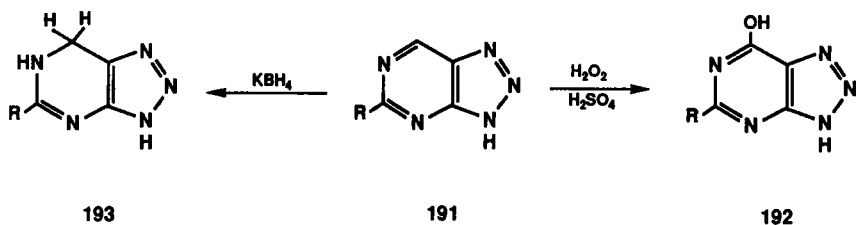
#### 4. Ring-Opening Reactions

Derivatives of the 1,2,3-triazolo[4,5-*d*]pyrimidine **42**, with no substituent on the 7-position, form stable 6,7-adducts **198** with activated methylene compounds [72JCS(P1)457]. When one (or both) of the activating groups was cyano, a ring-opening that involved scission of the 6,7-bond reaction occurred. Here, **42** and **191** have been treated with ethyl cyanoacetate to give 5-aminomethyleneamino-, 5-diaminomethyleneamino-, 5-thioureido-, and 5-ureido-4-(2-cyano-2-ethoxycarbonylvinyl)-1,2,3-triazoles **199a,b** and **200a,b**, respectively, and with malononitrile to give the 4-(2,2-dicyanovinyl)-1,2,3-triazoles **199c,d** and **200c,d**, respectively. The triazoles can be cyclized either to the starting triazolopyrimidine or to 5-amino-6-cyano-1,2,3-triazolo[4,5-*b*]pyridine by the action of alkali [73JCS(P1) 1620] (Scheme 41).

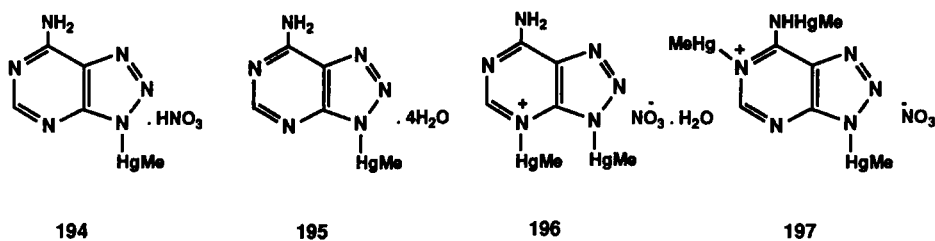
Reaction of **201** with 1,3-dicarbonyl compounds, or with aliphatic and cyclic ketones **203** in the presence of dilute sulfuric acid, gave the 3*H*-1,2,3-triazolo[4,5-*b*]pyridines **204** (79CPB2861). The mechanism of transformation involves ring fission to **202**, followed by reaction with **203** to give **204**, a type of Friedlaender synthesis (see Scheme 42).

The ring fission of the triazolopyrimidine **201**, prepared by the catalytic hydrogenation of **205** with Pd-MgO by the action of warm sodium hydroxide or dilute sulfuric acid, gave the triazole carboxaldehyde **202** (79MI1). When methanolic solutions of **201** and **202** in sodium methoxide were allowed to stand for 2 weeks at room temperature, **206** and **207** were obtained, respectively. The 7,7'-bistriazolopyrimidine **206** also was obtained by the action of cyanide ion on **201** (79CPB2431) (Scheme 43).

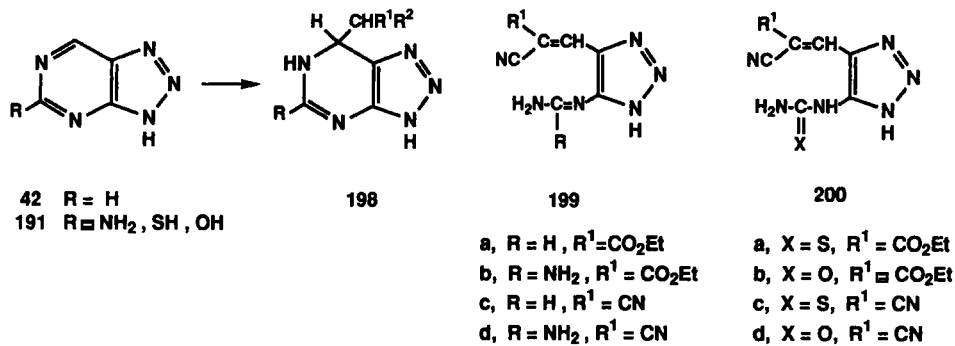
Elimination of nitrogen from the triazolo[4,5-*d*]pyrimidine **208** took place on the reaction with BuLi followed by MeCHBrCONH<sub>2</sub> to afford the bisalkylated pyrimidine **209** (90TL6103) (Scheme 44).



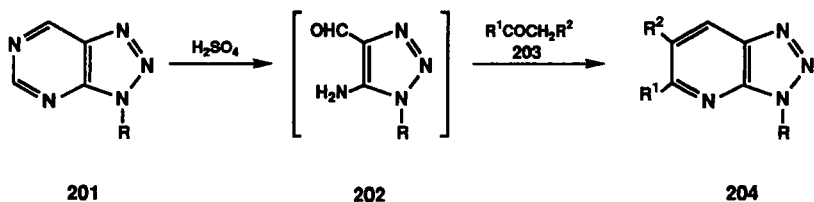
SCHEME 39



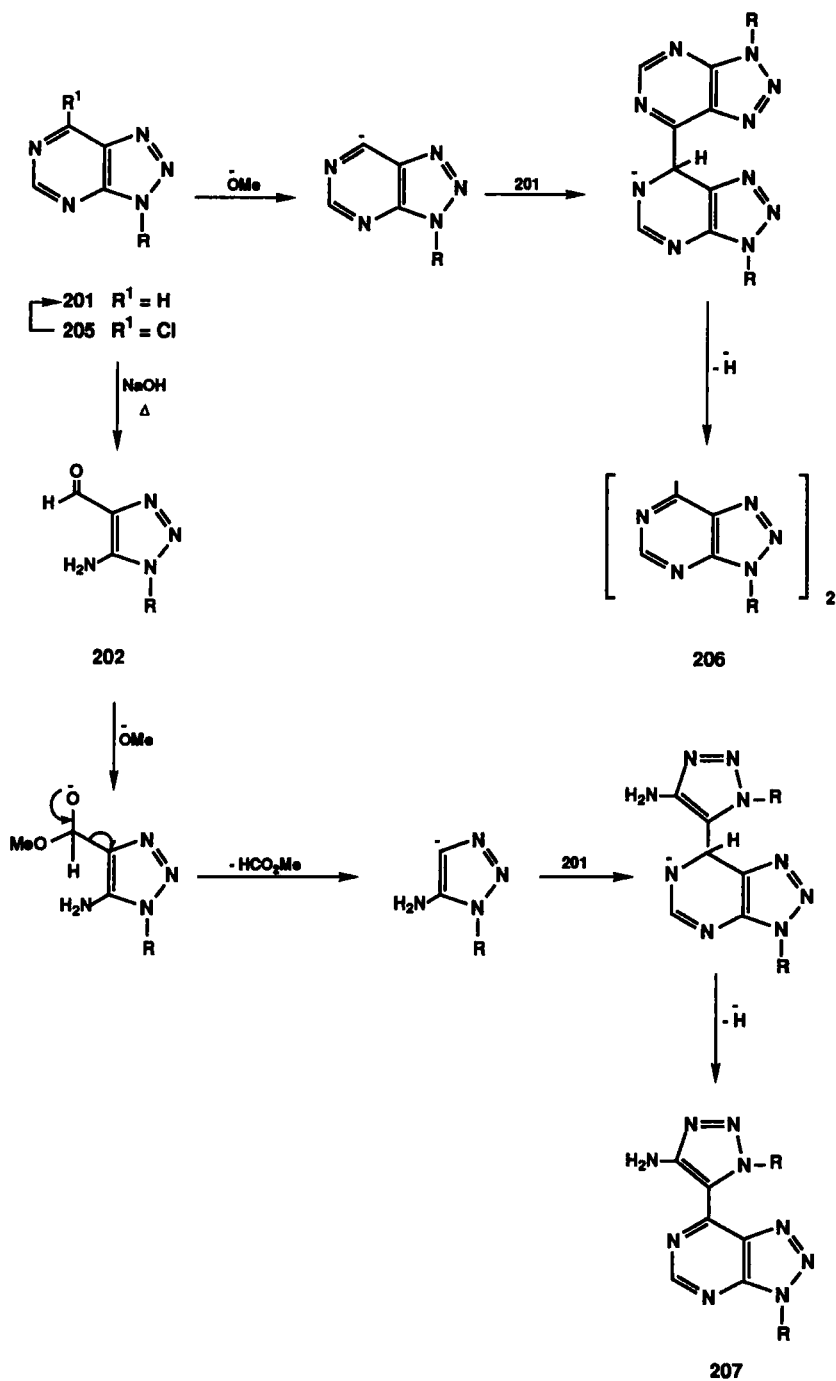
SCHEME 40



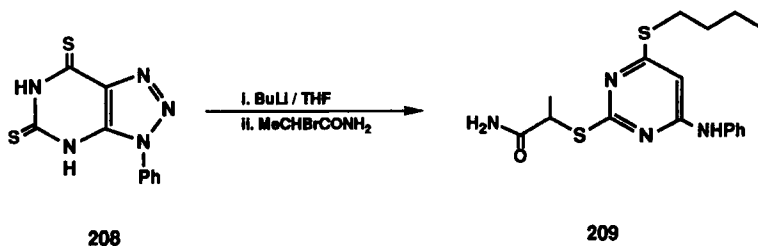
SCHEME 41



SCHEME 42



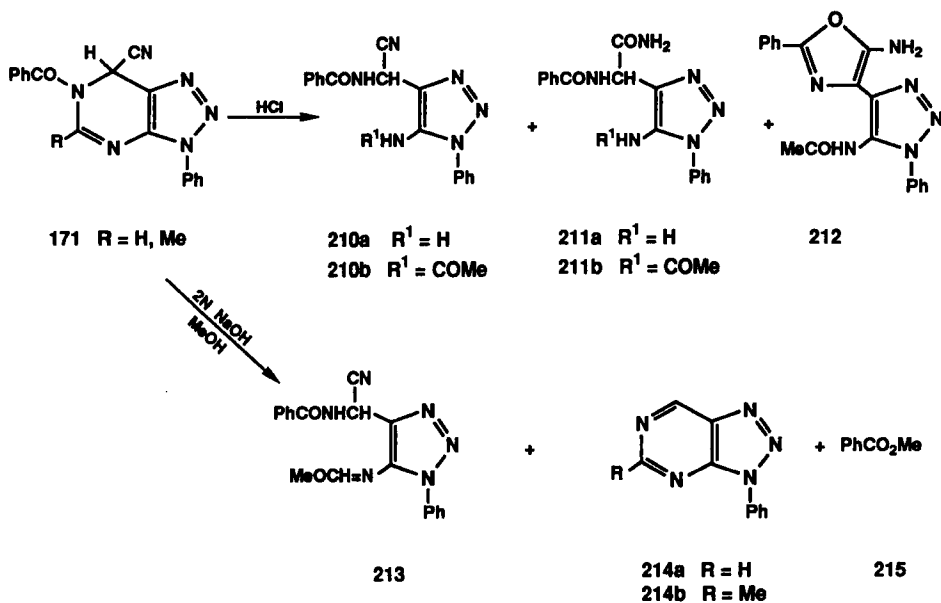
SCHEME 43



SCHEME 44

Treatment of 6-benzoyl-6,7-dihydro-3-phenyltriazolopyrimidine-7-carbonitrile (**171**, R = H) with acid caused fission of the pyrimidine ring to give the triazole derivatives **210a** and **211a**, but the 5-methyl derivative (**171**, R = Me) gave the triazoles **210b**, **211b**, and **212**. Alkaline hydrolysis of **171** (R = Me) with 2 N sodium hydroxide gave the triazolopyrimidine **214b** and methyl benzoate (**215**). In contrast, **171** (R = H) underwent ring fission to give  $\alpha$ -benzamido-5-(methoxymethleneamino)-1-phenyltriazole-4-acetonitrile (**213**), together with **214a** and **215** (92CPB513) (Scheme 45).

Pyrolysis of the triazolo[4,5-*d*]pyrimidine **42** did not give the expected cyanoimidazole **216**, but the only identifiable products were HCN and ammonia due to the fragmentation of the pyrimidine ring (70T3965).



SCHEME 45

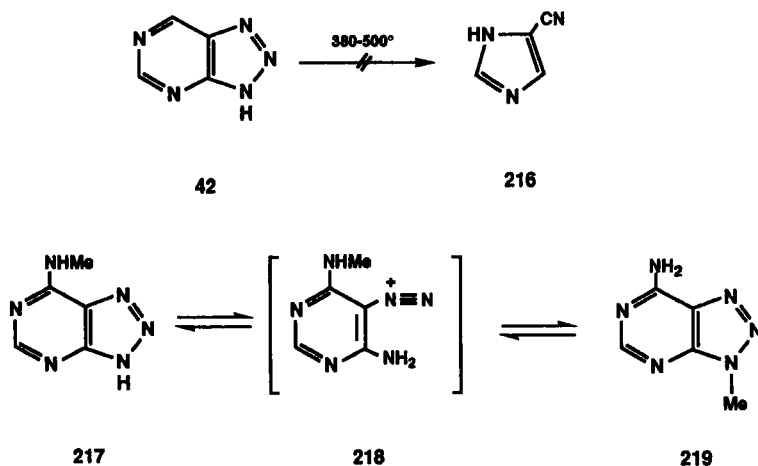


The Dimroth equilibration of **217**  $\rightleftharpoons$  **219** via the ring-opened intermediate **218** took place on heating at 150°C in DMF or fusion at 290°C [74 JCS(P1)2030] (Scheme 46).

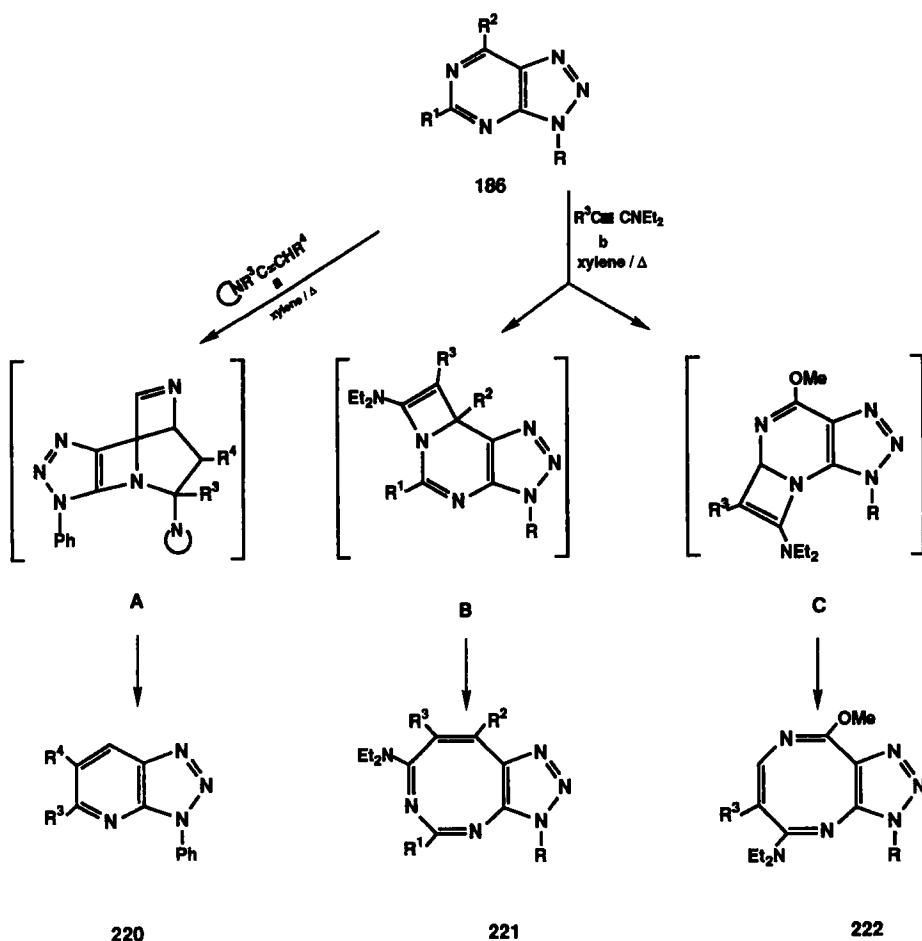
A [4 + 2]-cycloaddition of 3*H*-1,2,3-triazolo[5,4-*d*]pyrimidine **186** (R = Ph; R<sup>1</sup> = R<sup>2</sup> = H) and enamine **a** gave the 3*H*-1,2,3-triazolo[4,5-*b*]pyridines **220** through a selective addition across the N-4-C-7 bond of the ring followed by successive loss of hydrogen cyanide and amine from the initial cycloadduct **A**. On the other hand, the ynamine **b** added selectively across the N-6-C-7 double bond in **186**, followed by isomerization of the resulting [2 + 2]-cycloadduct **B** into the 3*H*-1,2,3-triazolo[4,5-*d*][1,3]diazocines **221**. However, in the case of the 7-methoxy derivative **186** (R<sup>1</sup> = H; R<sup>2</sup> = OMe), the nucleophilic carbon of ynamine **b** selectively attacked the C-5 ring carbon rather than the C-7 to give 3*H*-1,2,3-triazolo[4,5-*d*][1,5]diazocines **222** by way of the intermediate [2 + 2]-cycloadduct **C** (91CPB282) (Scheme 47).

### 5. Nucleoside Analogs

The starting material for the synthesis of acyclic (90JHC1409) and carbocyclic nucleoside analogs (81USP4268672; 84JMC670; 84JMC1416; 88USP4728736; 90EUP368640; 90JMC17; 90JMC1214; 91EUP410660) was 2-amino-4,6-dichloropyrimidine (**223**), whose condensation with cyclopentylamine derivatives, 3-amino-1,2-propanediol, or 4-amino-1-butanol gave **224**. Reaction of **224** with a diazonium chloride gave **225**, whose subsequent reduction with zinc in acetic acid afforded **226**, which upon reaction



SCHEME 46



SCHEME 47

with nitrous acid gave **227**. Reaction of **227** with thiourea in *n*-butanol and with aqueous hydrochloric acid gave 8-azathioguanosine **228** and 8-azaguanosine **229** respectively (90JHC1409). Reaction of **227** with ammonia gave the diamino derivative **231** (84JMC1416). The corresponding 5-dimethylamino derivatives were obtained through amination with dimethylamine [85IJC(B)952; 88EUP288431].

Diazotization of (5-amino-6-chloropyrimidin-4-yl-amino)cyclopentane derivatives followed by acid hydrolysis yielded the 8-azahypoxanthine **230** without isolation of the 6-chloropurine derivatives, whereas treatment with anhydrous ammonia gave the 8-azaadenosine **232** (73JHC601; 73JPS858) (Scheme 48).



The diol in the 9-cyclopentyl-8-azaadenosine analog **232** can be protected as an acetonide whose treatment with  $\text{NaH-H}_2\text{NSO}_2\text{Cl}$  followed by deacetonation furnished the 5'-sulfamoylated derivative (92JMC3991). Phosphorylation of the acetonide with  $\text{POCl}_3$  in  $\text{Me}_3\text{PO}_4$  followed by hydrolysis gave the phosphate derivative, which was cyclized with dicyclohexylcarbodiimide to the cyclic monophosphate analog **233** (73JHC601).

Condensation of **234** with 5-amino-4,6-dichloropyrimidine (**91**) gave **235**, whose reaction with nitrous acid followed by treatment with ammonium hydroxide gave the carbocyclic analog **236** (84JMC1358) (Scheme 49).

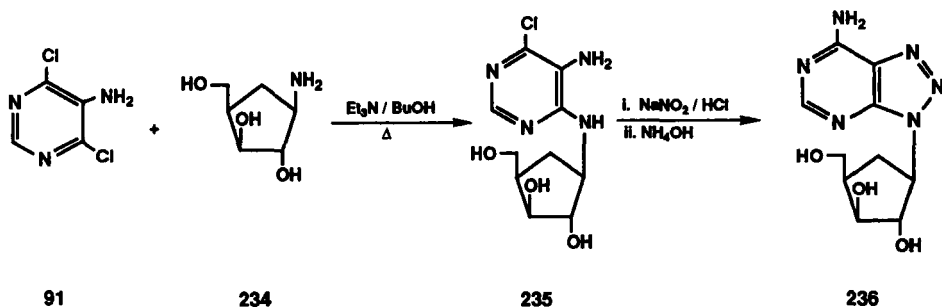
Reduction of the nitro group in clitocine analogs **237** followed by nitrous acid cyclization gave the azanucleosides **238**, whose deprotection with  $\text{BCl}_3$  afforded **239** (93JHC1393) (Scheme 50).

A series of 3-glycosyl-1,2,3-triazolo[4,5-*d*]pyrimidines **241** was prepared by treatment of amino(glycosylamino)pyrimidines **240** with nitrous acid. Acetylation of **241** gave **242**, whose desulfurization gave 9-glycosyl-8-azahypoxanthines **243** (84MI1; 91JHC1417) (Scheme 51).

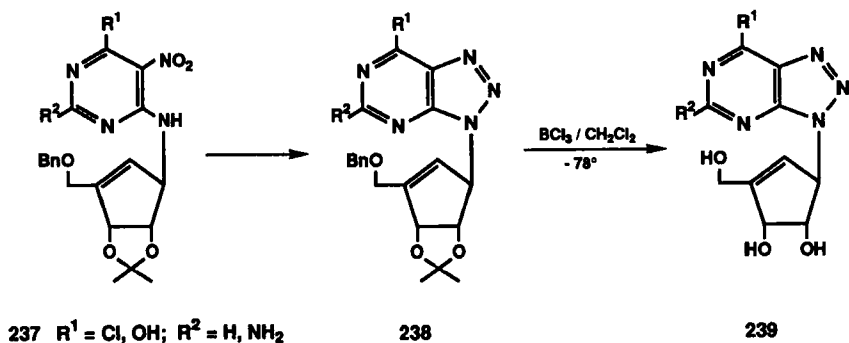
The 9- $\alpha$ -L-rhamnopyranosyl derivative **246** has been synthesized by the condensation of the 2,3,4-tri-*O*-benzoyl-L-rhamnopyranosylbromide (**245**) with chloromercuric complex **244**. Deblocking of **246** with methanolic ammonia gave the 8-azaadenosine **247** [84IJC(B)369] (Scheme 52).

The synthesis of 5-amino-3- $\beta$ -D-ribofuranosyl-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (8-azaguanosine) (**250**) has been achieved by glycosylation of silylated 8-azaguanine **248** with 2,3,5-tri-*O*-benzoyl-D-ribose bromide to give the benzoylated nucleoside **249**, which was subsequently deblocked to **250**. Deamination of **250** with  $\text{HNO}_2$  gave 8-azaxanthosine **253**. Fusion of the silylated derivative of **248** with 2-deoxy-3,5-di-*O*-toluoyl-D-erythro-pentofuranosyl chloride followed by deblocking gave the anomeric nucleosides **251** and **252** (72JMC879) (Scheme 53).

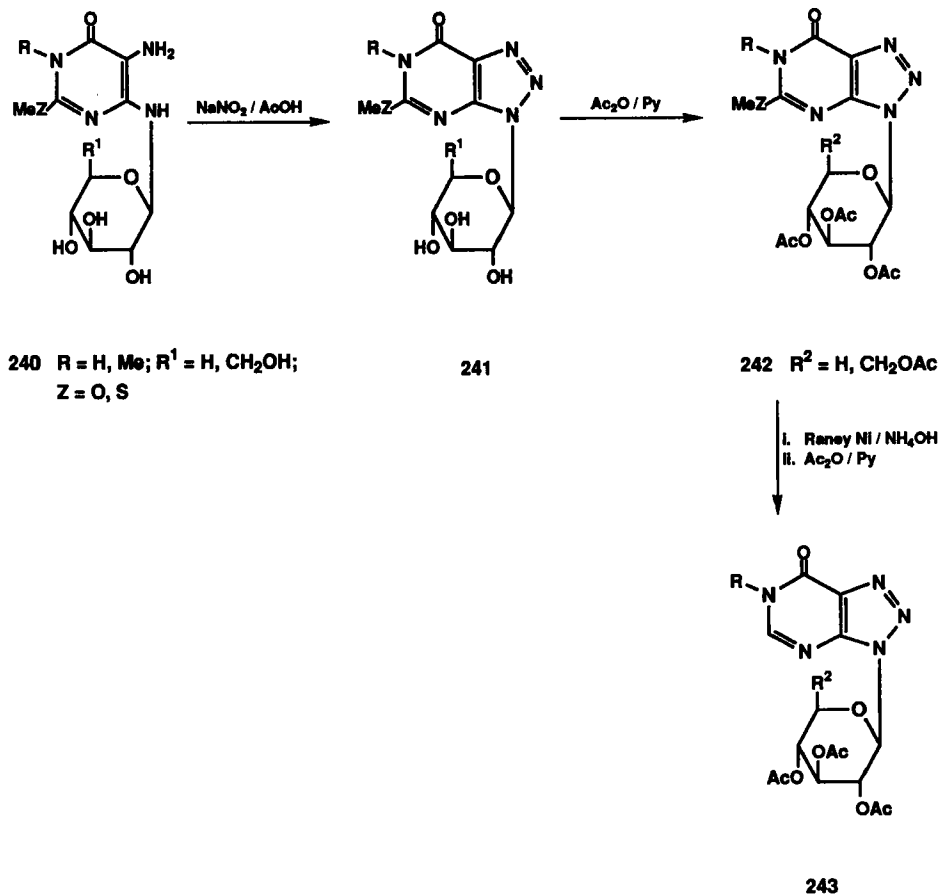
Acid-catalyzed fusion of 7-methylthio-1,2,3-triazolo[4,5-*d*]pyrimidine (**257**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**254**) gave the



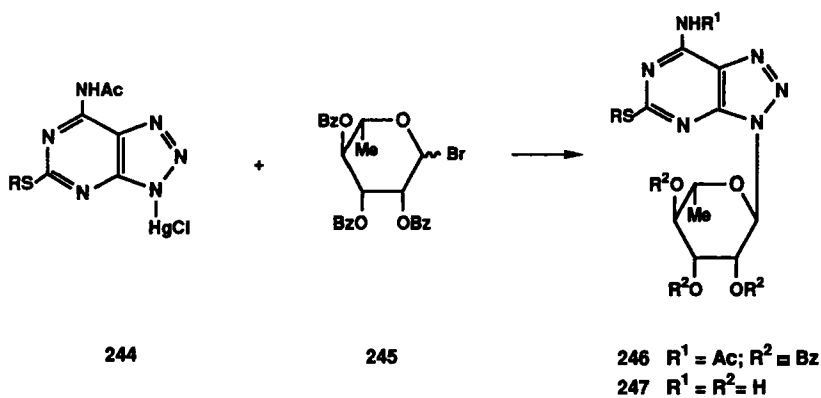
SCHEME 49



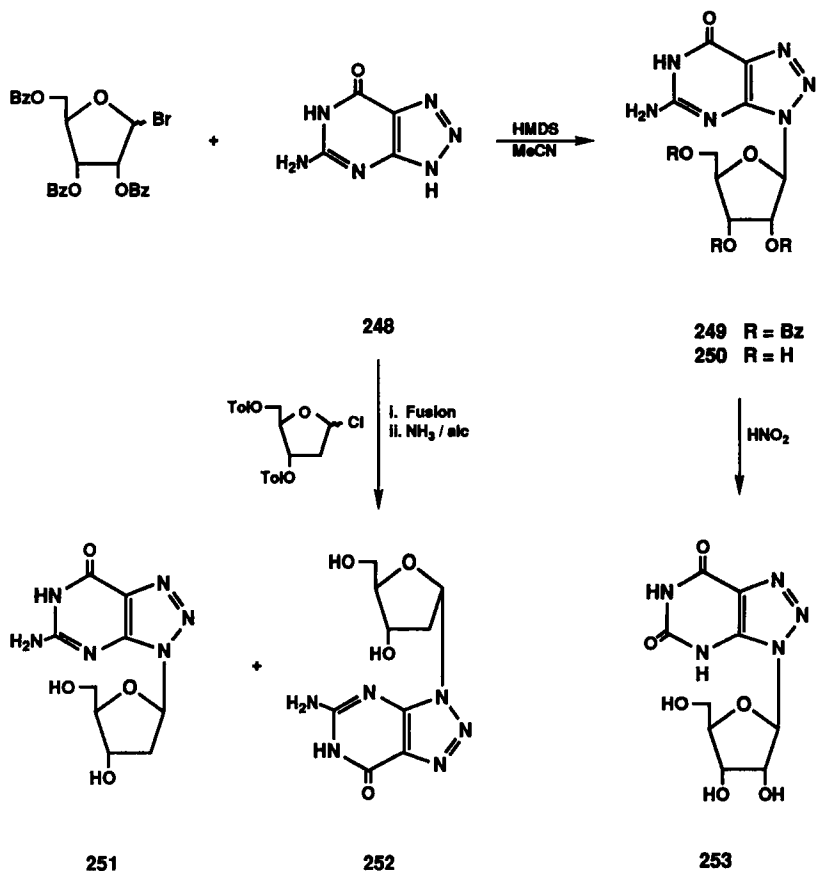
SCHEME 50



SCHEME 51



SCHEME 52



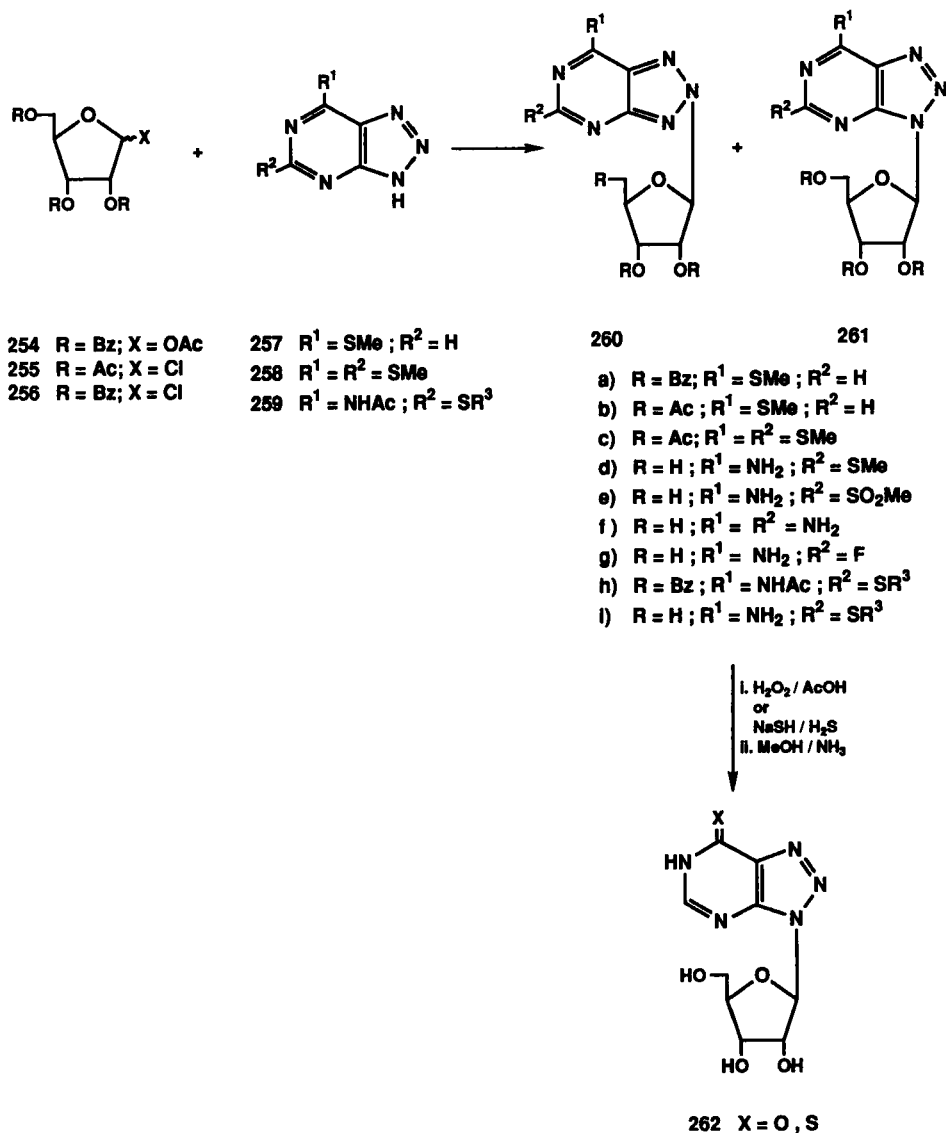
SCHEME 53

purine analogs **260a** and **261a** (70IJ919). Ribosylation of **257** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride (**255**) afforded a 1 : 2 mixture of **260b** and **261b**; after the mixture was heated in toluene in the presence of molecular sieves, the ratio became 1 : 6 (78MI2; 91EUP409227).

Treatment of **261b** with  $\text{H}_2\text{O}_2$ -AcOH or NaSH- $\text{H}_2\text{S}$  followed by de-blocking furnished the 8-azainosine or the thioinosine derivatives **262** (70IJ919; 72JMC879). Fusion of **258** with tetraacetylribofuranose in the presence of a trace of *p*-toluenesulfonic acid afforded a mixture of nucleosides with about a 2 : 3 ratio of **260c** and **261c**. In addition, small amounts of 8- and 9-substituted  $\alpha$ -anomers were present (83JMC1483). Molecular sieves catalyzed coupling of 2,6-bis(methylthio)-8-aza-9*H*-purine (**258**) with **255** in toluene to give **260c** and **261c**, with about a 1 : 7.5 ratio. No HPLC conditions were found to separate them (70IJ919; 72JMC879). Their treatment with ethanolic ammonia to effect displacement of the 6-methylthio group produced the 8-substituted isomer **260d** and the 9-substituted isomer **261d**. To facilitate incorporation of an amino group at C-2 in 8-azapurine nucleosides, the methylthio substituent was oxidized with *m*-chloroperbenzoic acid to a methylsulfonyl as in **260e** and **261e**. Displacement of the methylsulfonyl group occurred readily upon treatment with ethanolic ammonia to give **260f** and **261f**, which upon treatment with aqueous fluoroboric acid-potassium nitrite produced the fluoro compounds **260g** and **261g** (83JMC1483). Condensation of the tribenzoylribosyl chloride **256** with **259** in the presence of  $\text{HgCl}_2$  yielded only 6-acetamido-2-alkylthioriboside **260h**, which upon deprotection with methanolic ammonia gave **260i** [84IJC(B)369] (Scheme 54).

Glycosylation of the anion of 7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**263**) with **264** yielded three regioisomeric protected *N*-2, *N*-3, and *N*-4-(2'-deoxy- $\beta$ -D-ribofuranosides) together with nearly equal amounts of their  $\alpha$ -D-anomers, **265**, **267**, and **269** respectively. The reaction became stereoselective for the  $\beta$ -D-nucleosides when the anion of 7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine **270** was glycosylated with **264** in MeCN. Only the *N*-2, *N*-3, and *N*-1-(2'-deoxy- $\beta$ -D-nucleosides) **271**-**273** were obtained. Treatment of **271**-**273** with ammonia afforded the amino nucleosides **266**, **268** and **274**, respectively. The anomeric configuration and the position of glycosylation were determined by combination of  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and 1D NOE difference spectroscopy (89HCA1527; 93HCA2388) (Scheme 55).

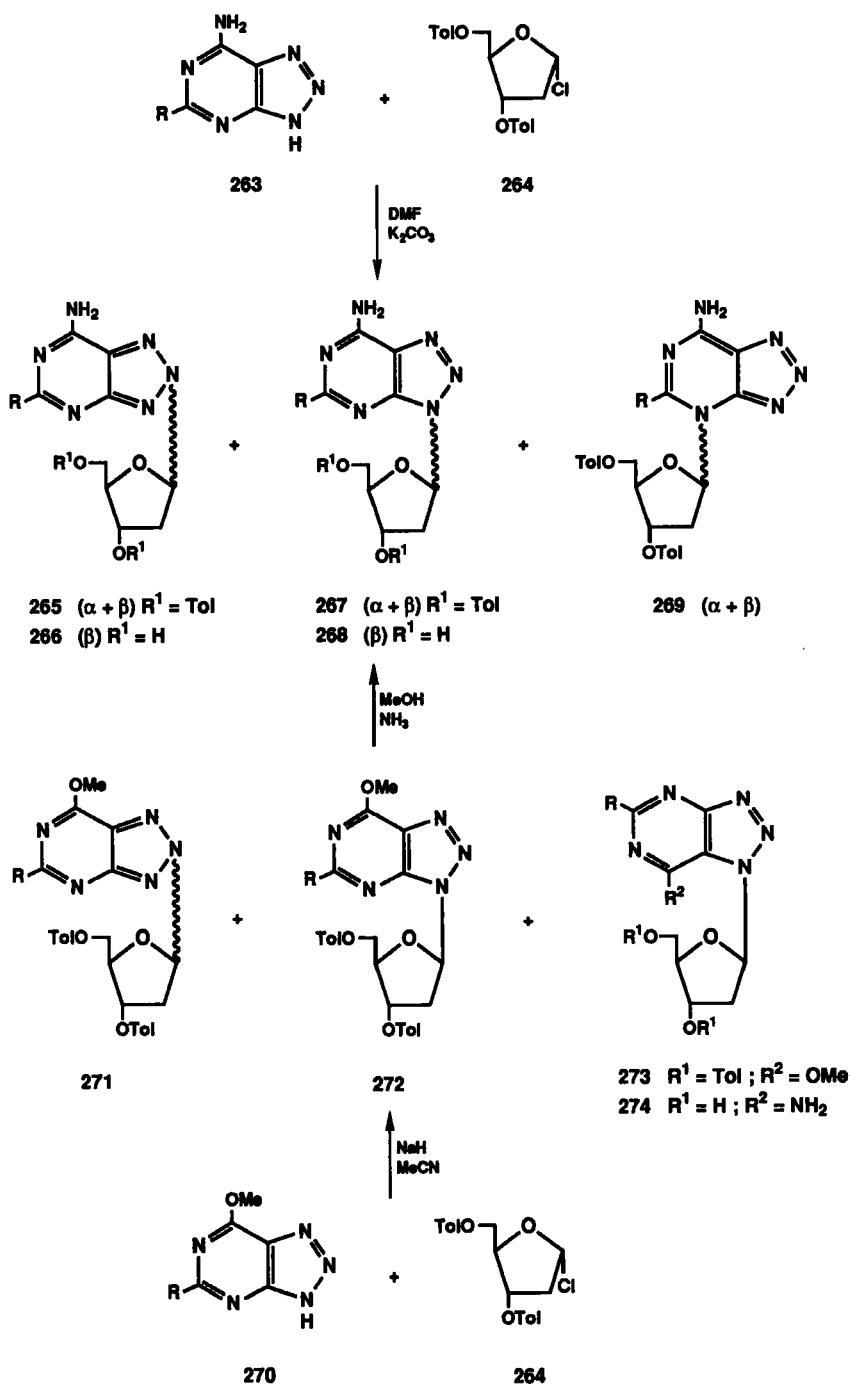
The synthesis of the dideoxyribonucleosides was achieved by glycosylating the anion of **275** with 5-*O*-[(*t*-butyl)dimethylsilyl]dideoxypentofuranosyl chloride (**276**) to give the regioisomeric nucleosides **277**-**279**. Treatment of the desilylated products **280**-**282** with aqueous NaOH gave



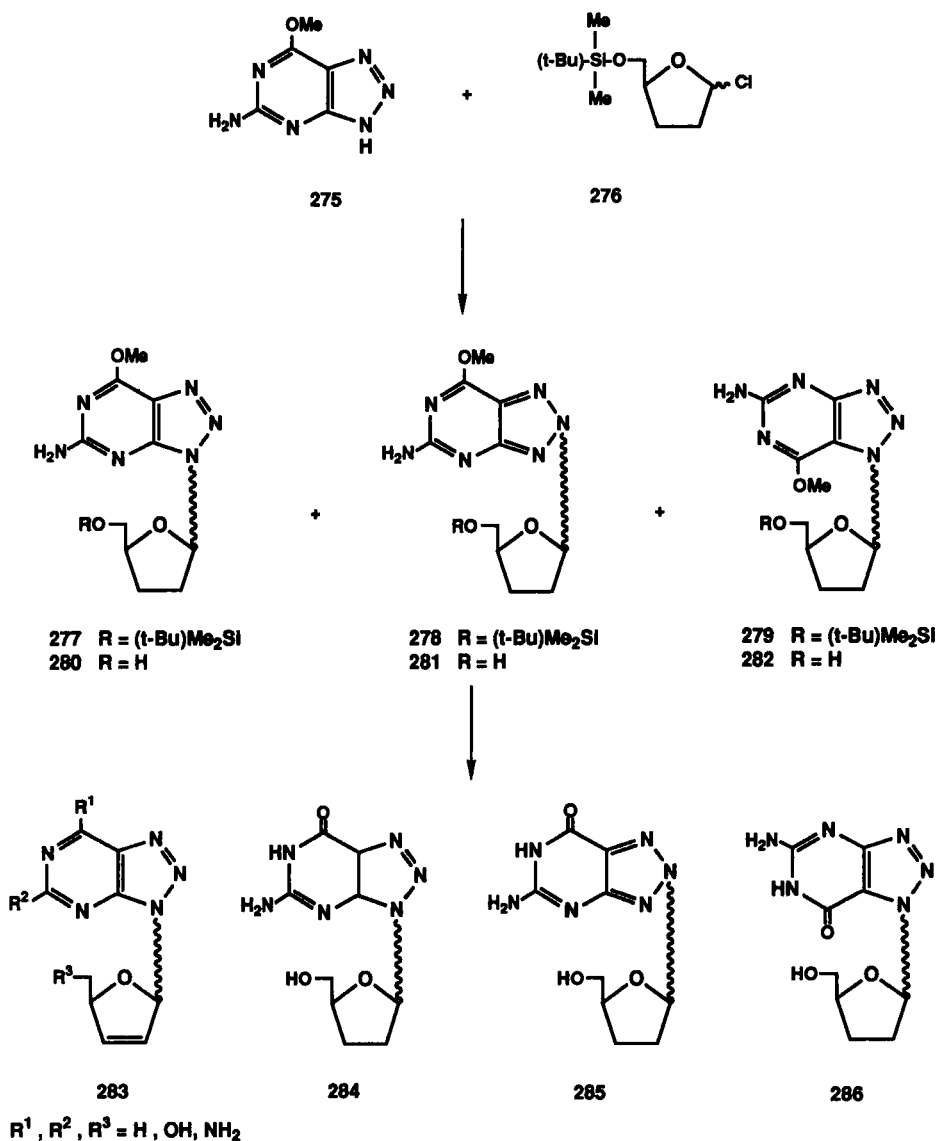
SCHEME 54

the corresponding regioisomers **284–286**. Amination of **280** gave the di-amino derivative, which upon phosphorylation gave the corresponding 5'-triphosphate (92HCA1885; 93HCA2184). The 2',3'-unsaturated nucleosides **283** were also prepared (91GEP296281) (Scheme 56).



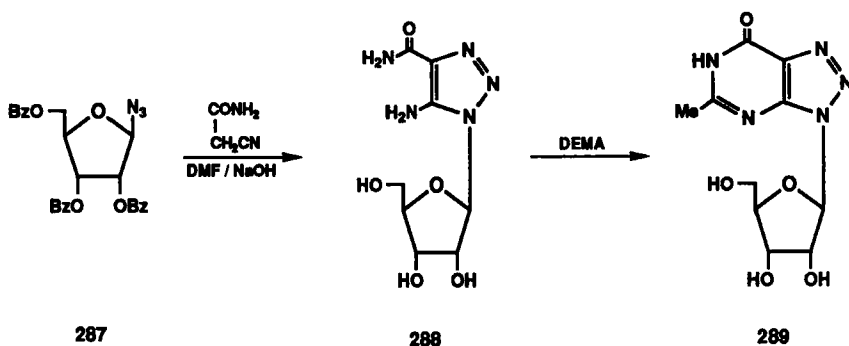


SCHEME 55



SCHEME 56

Ring closure of the azide **287** with cyanoacetamide gave the triazole **288**, whose cyclization with diethoxymethyl acetate (DEMA) gave **289** (72JMC879). The protecting group in **287** can be also an isopropylidene instead of the benzoyl groups (92FA525) (Scheme 57).



SCHEME 57

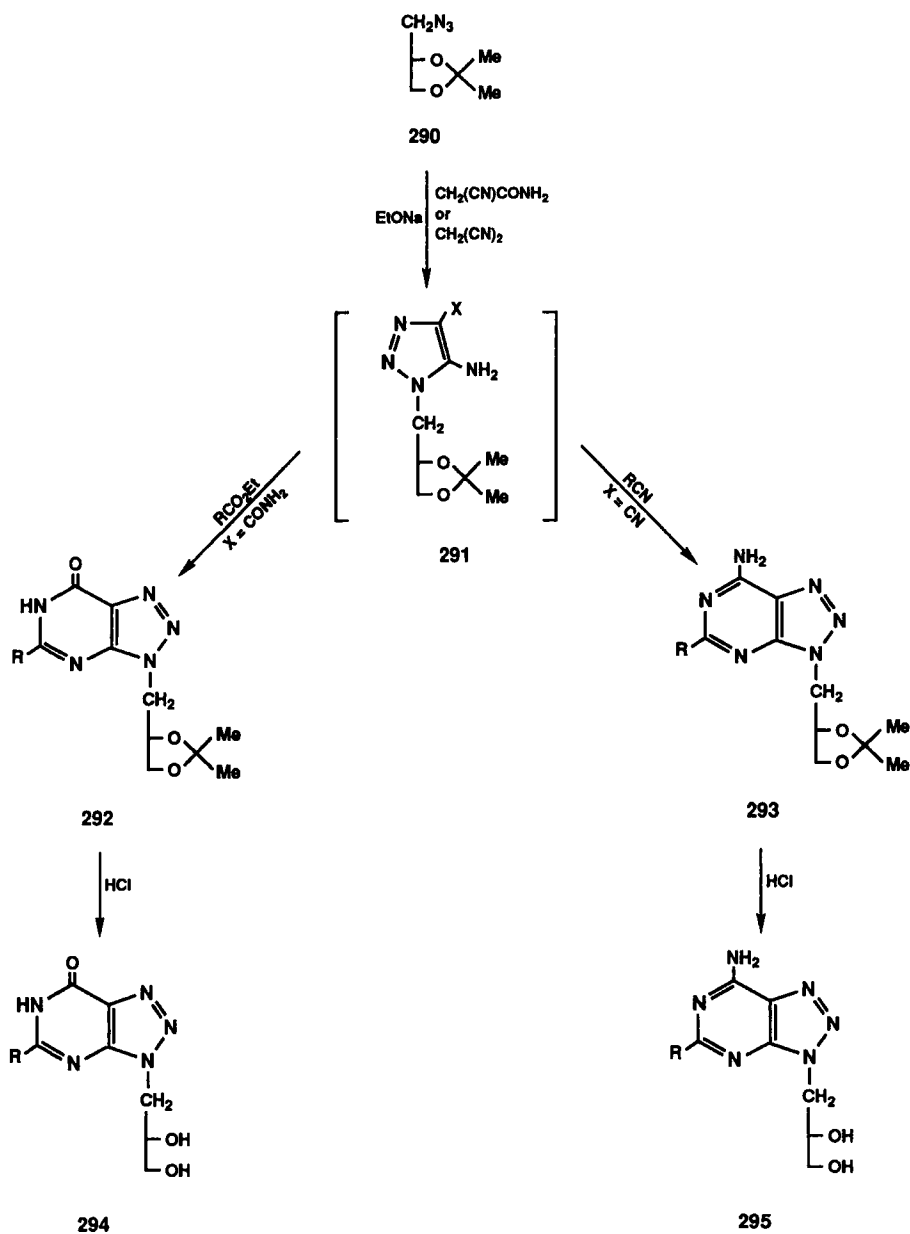
1,3-Dipolar cycloaddition of the sodium salt of cyanoacetamide or malononitrile to the acetonide of racemic or optically active 1-azido-2,3-dihydroxypropane **290** afforded the intermediate triazoles **291**, which were converted directly to the 2-substituted 9-(2',3'-dihydroxypropyl)-8-azahypoxanthines **294** and 8-azaadenines **295** by treating with a suitable ester or nitrile to give the isopropylidene derivatives **292** and **293**, respectively, followed by acid hydrolysis. The percentage of racemization was determined by NMR with the Europium shift reagent  $[\text{Eu}(\text{tfc})_3]$  (91JHC1351) (Scheme 58).

The 2-amino-8-azapurine **298** was prepared by heating **296** with  $(\text{Me}_3\text{Si})_2\text{NH}$  in the presence of ammonium sulfate followed by treatment with  $\text{ClCH}_2\text{OCH}(\text{CH}_2\text{OCHMe}_2)_2$  in triethylamine to give **297**, whose desilylation gave **298** (89EUP298467). 8-Azaguanine nucleosides containing (2-hydroxyethoxy)methyl- or [2-hydroxy-1-(hydroxymethyl)ethoxy]methyl moieties at N-9 were also prepared (85JMC982; 86EUP201289) (Scheme 59).

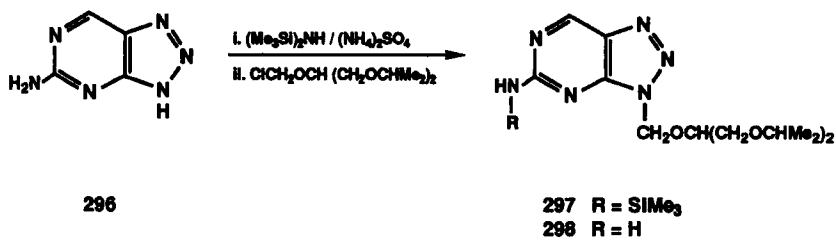
The kinetics and mechanism of acid-catalyzed hydrolysis of regioisomeric 8-azaadenine 2'-deoxyribofuranosides **299a-e** have been determined over a wide pH range. The mechanism involved a rapid initial protonation of the base moiety of **299** and a rate-limiting unimolecular cleavage of the N-glycosidic bond to give the free base and a cyclic glycosyloxocarbenium ion [91JCS(P2)595] (Scheme 60).

## 6. Biological Properties

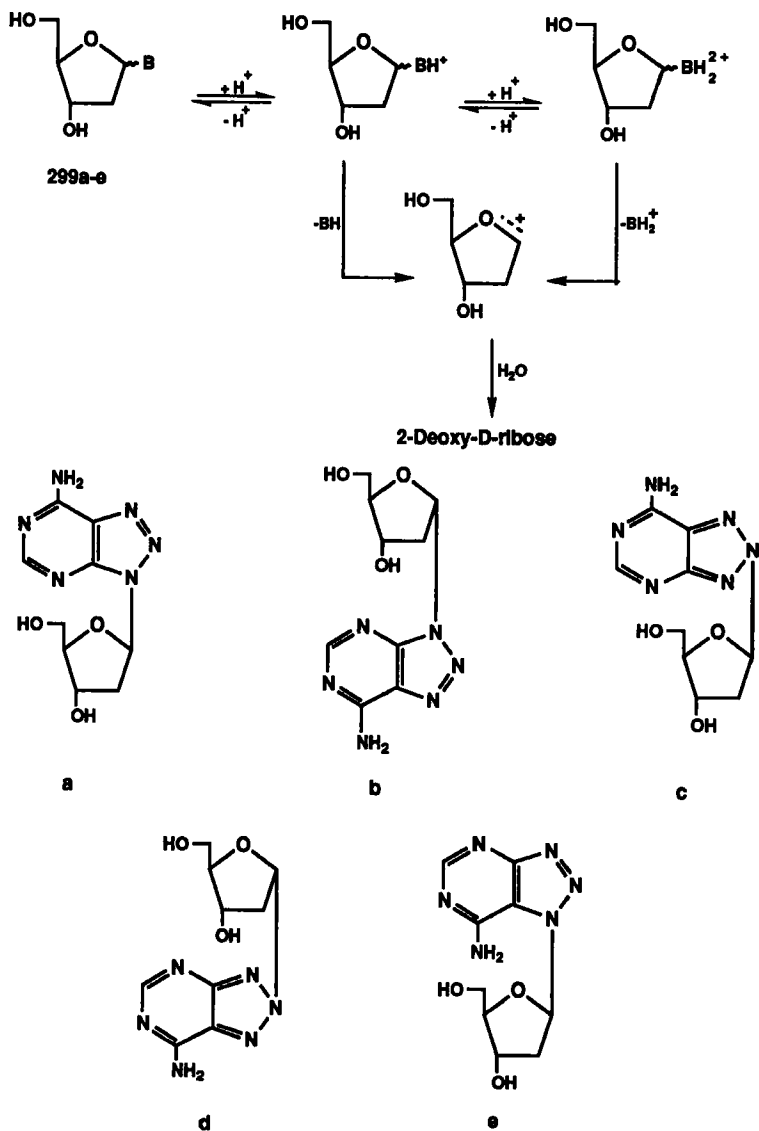
9-Aryl-8-azaadenines **300**, 8-azahypoxanthine **301**, and 6-thio-8-azapurines **302** were tested for their inhibitory effect on adenosine deaminase, guanine deaminase, and xanthine oxidase from mammalian sources. Compounds **300** were the most efficient inhibitors of adenosine deaminase and



SCHEME 58



SCHEME 59

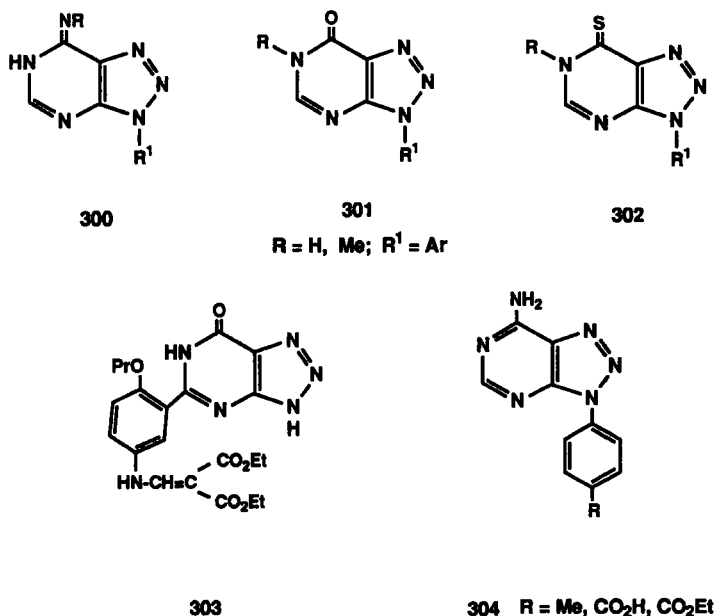


SCHEME 60

xanthine oxidase. Methylation at C-6 in **300** lowered the affinity of the compound for the enzyme. Compounds **301** were very powerful inhibitors of xanthine oxidase and low efficient inhibitors of adenosine deaminase. Compound **302** had a low inhibitory effect on adenosine deaminase (82MI1). The 8-azaadenine **138**, bearing three lipophilic groups on the 8-azaadenine nucleus, revealed moderately good activity toward adenosine A<sub>1</sub> receptors (94FA93, 94FA183, 94FA187). The debenzylated derivatives of **135** showed inhibitory activity against xanthine oxidase (87JHC997) (Scheme 61).

The hydroxyl group bonded to a chiral carbon atom in compound **134** represents a possible site for the formation of a stable enzyme-inhibitor complex with adenosine deaminase (ADA), as in *S*-9-(2'-hydroxypropyl) adenine and its 1'-alkyl derivatives. Moreover, the influence of the nitrogen atom on C-3' regarding the inhibitory activity against ADA deserves further investigation. The substituent on C-2 of the nucleus constitutes the third structural element, whose influence on the biological activity of the molecule must also be considered (89JHC39).

Restricted rotation has been observed in **151**, indicating two possible orientations of the hydrophobic cyclopentyl group relative to the plane of the heterocyclic ring of adenosine receptor ligands (91TL3583). Compound **268**



SCHEME 61

proved to be a substrate for adenosine deaminase, whereas the regioisomers **266** and **274** were not deaminated (89HCA1527; 93HCA2388).

The 5'-alkynyl(cyano) derivatives of adenosine **274** and its carbocyclic analog derivatives **231** and **232** were examined as inhibitors of *S*-adenosyl-L-homocysteine and *S*-adenosyl-L-methionine hydrolase (89EUP334361).

Nucleosides in Scheme 54 were evaluated for cytotoxicity, adenosine deaminase activity (83JMC1483), and activity against hepatitis B virus (91EUP409227).

The 8-aza analogs of the potent antiviral nucleotide analogs 9-[2-(phosphonmethoxy)ethyl]adenine (PMEA) and 9-[2-(phosphonmethoxy)ethyl]guanine (PMEG) were evaluated for activity against human immunodeficiency viruses (94MI3).

The acyclic 8-azaguanine nucleosides having (2-hydroxyethoxy)methyl- or [2-hydroxy-1-(hydroxymethyl)ethoxy]methyl moieties at N-9 were screened against herpes simplex virus type 1 (HSV1) (85JMC982; 86-EUP201289).

The rhamnopyranosyl nucleoside **247** was proposed as antiviral agent [84JCB(B)369]. 2-Amino-8-azaadenosines **231** and their corresponding 6-dimethyl derivatives are active against herpes simplex virus type 1,2 (HSV-1,2). Some of them were evaluated for both antitumor and antiviral activity, as well as activity against influenza and human immunodeficiency viruses (HIV) (81USP4268672; 84JMC1416; 85USP4543255; 90JMC1214).

8-Azaguanine has been used for producing human-mouse hetero hybridomas by fusion of human myeloma (RPM 18226) with mouse myeloma (FO) [91JAP(K)03183477].

Replacement of the two chlorine atoms in 3-phenyl-5,7-dichloro-1,2,3-triazolo[4,5-*d*]pyrimidine gave 3,5,7-trisubstituted triazolopyrimidine derivatives [84JAP(K)5962595], which showed anticarcinogenic activity against sarcoma tumor cells in mice. Compounds **159** have been used as anticarcinogenics [81JAP(K)8131586, 81JAP(K)8131587].

The nucleosides **236** were evaluated for cytotoxicity on mouse lymphoid leukemia cells (84JMC1358). Compounds **242** were screened for their anticancer or anti-AIDS activities (91JHC1417). Anticarcinogen activity against sarcoma 180 ascite tumor cells in mice was shown by **90** [84JAP(K)5962593].

The 1,2,3-triazolopyrimidine **303** has an antianaphylactic activity five times greater than that of 5-(*o*-propyloxyphenyl)-1,2,3-triazolo[4,5-*d*]pyrimidine-6*H*-7-one, which allows it to be used in the treatment of hypertension and congestive heart failure or edema resulting from hypertension (82SWP627755; 90USP4923874). Compounds **304** have been tested for central nervous system, analgesic, anti-inflammatory, and antiallergic activities (80FES308). Some antiallergic activity has been exhibited by **117**, but

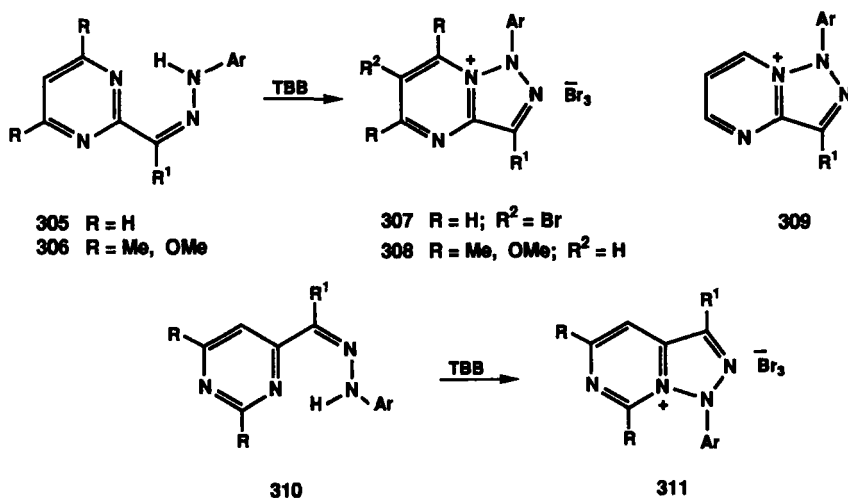
it showed no central nervous system, analgesic, or anti-inflammatory activities (80FES298). Compounds **116** have been tested as inhibitors of xanthine oxidase. The inhibitory activity was dependent on the length of the alkoxy chain. Compound **148** has antibronchospastic activity (88EUP 272226).

## Appendix

The literature (*Chemical Abstracts* volumes **122** and **123**) that became available to us after this review was written is discussed here.

### RING SYNTHESIS

1,2,3-Triazolo[1,5-*a*]pyrimidinium salts **307** and **308** have been synthesized via cyclodehydrogenation of the appropriate pyrimidyl ketone arylhydrazones **305** and **306**, respectively, using 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one (TBB). The pyrimidine ring in **305** was simultaneously brominated during ring closure, but bromination failed in the case of **306**, probably because of the steric hindrance of the substituents. To avoid the bromination of **305**, a dilute solution of TBB in  $\text{CH}_2\text{Cl}_2$  was used to give **309** (94JHC1041). 1,2,3-Triazolo[1,5-*c*]pyrimidinium perbromide **311** was prepared by oxidation of **310** (94JHC1041) (Scheme 62).



SCHEME 62





compound and its analogs, 1,3-dimethyl-2-thio-8-azaxanthine, 3-methyl-8-azaxanthine, and 3-methyl-2-thio-8-azaxanthine, and their anionic forms with the MOPAC program. The most stable tautomer is *N*-7-H for the neutral compounds. For the hydrogen-bonded dimer, a stabilization energy of  $-19.76 \text{ kcal mol}^{-1}$  has been computed, which may explain why the *N*-8-H tautomer is found in the solid state (95JST257).

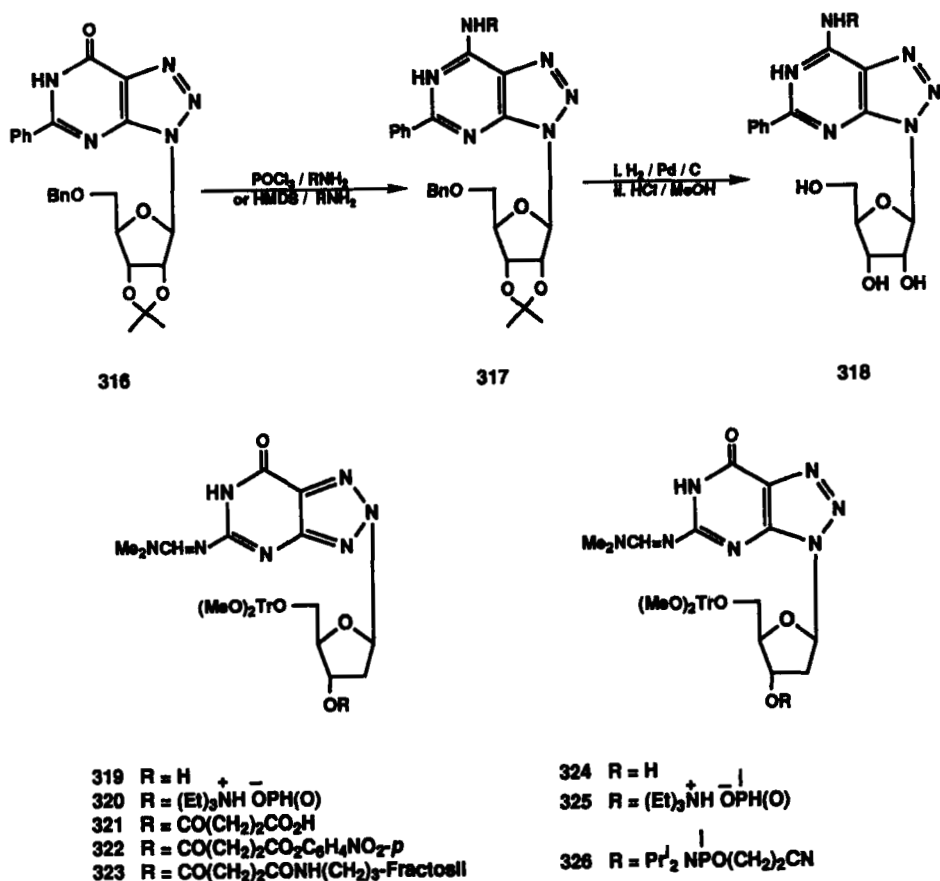
### NUCLEOSIDE ANALOGS

The 8-azahypoxanthine derivative **316** was prepared in a manner similar to that of **289** (95FA13). Reaction of **316** with phosphorus oxychloride or HMDS followed by amination gave the 8-azaadenosine **317**, which upon deprotection gave **318** (95FA13).

The phosphonate **320** was prepared from amidine **319** and  $\text{PCl}_3$ -*N*-methylmorpholine/1*H*-1,2,4-triazole. Amidine **319** was also transformed into the Fractosil-linked derivative **323** by treatment with succinic anhydride to give **321**, esterification with 4-nitrophenol to give **322**, and then reaction with aminopropyl-functionalized Fractosil (94HCA1003). Similarly, the phosphonate **325** was prepared by the reaction of **324** with  $\text{PCl}_3$ -*N*-methylmorpholine-1*H*-1,2,4-triazole. Phosphoramidite **326** was made using chloro(2-cyanoethyl)(diisopropylamino)phosphane (94HCA1003). The phosphonate **320** was used in an automated solid-phase oligonucleotide synthesis. The oligonucleotides were characterized by enzymatic and melting curves (94HCA1003) (Scheme 64).

The nucleophilic substitution of (3*S-trans*)-tetrahydro-5-(dimethoxymethyl)-3-furanol-4-methylbenzenesulfonate (**327**) by 8-azaadenine (**140**) afforded a mixture of **328** and **329**. Hydrolysis of the dimethyl acetals followed by reduction with  $\text{NaBH}_4$  yielded the isonucleosides **330** and **331**, respectively. The bis(2,2,2-trichloroethyl)phosphate of **330** was obtained by its reaction with bis(2,2,2-trichloroethyl)phosphorochloridates (94JMC3534). Reaction of **330** with (phenylmethoxy)alaninyl phosphorochloridate and with  $\text{POCl}_3$ -( $\text{MeO}$ ) $_3\text{PO}$  and  $(\text{Bu}_3\text{N})_4\text{P}_2\text{O}_7$  gave the corresponding 5'-phosphoramidate and 5'-triphosphate derivatives, respectively (see Scheme 65).

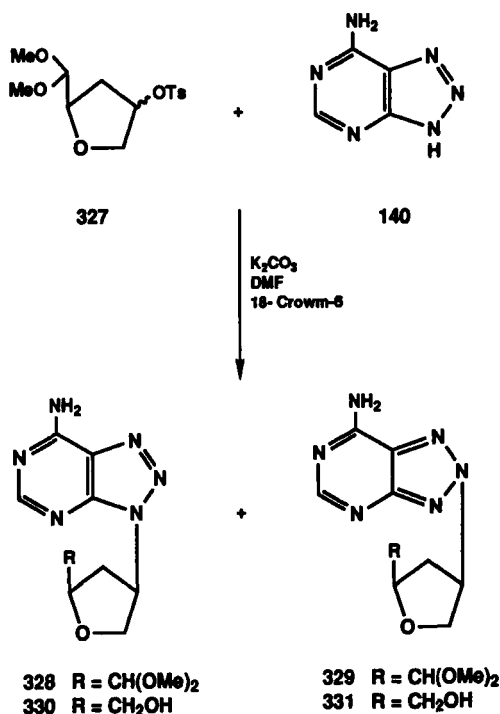
Alkylation of 8-azaguanine (**248**) with (*R*)- and (*S*)-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2-propanediol (**332**) in DMSO afforded a mixture of regioisomers *N*-7-, *N*-8-, and *N*-9-alkylated products **335**, **333**, and **334**, respectively. The 8-isomer **333** was separated from the mixture by flash chromatography. Deesterification of the mixture with bromotrimethylsilane in MeCN gave a mixture of phosphonates **337** and its 7-substituted isomer. After repeated crystallization, **337** was obtained as a pure compound. In a similar way, the *N*-8-alkylated derivative



SCHEME 64

**333** was converted into phosphonate **336** (95JMC4007). The (*R*)-8-aza analog of **337** was prepared from the reaction of 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone with the 1-amino analog of the (*R*)-isomer of **332** followed by reduction of the nitro group, cyclization to the guanine derivative, and then deprotection of the phosphate ester moiety (95JMC4007). Similarly, the enantiomeric acyclic nucleoside (*R*)-8-aza-8-[3-hydroxy-2-phosphonylmethoxypropyl] guanine (**338**) was prepared (95MI3) (Scheme 66).

The carbocyclic nucleoside analogs **342–344** were prepared by diazo coupling of (1*R*,*cis*)-3-pyrimidylaminomethyl-1,2,2-trimethylcyclopentyl-methanol (**339**) with 4-chlorobenzenediazonium chloride to give **340**, which upon reduction gave the triamine **341**. Ring closure of **341** with nitrous acid gave (1*R*,*cis*)-3-[(5-amino-7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-

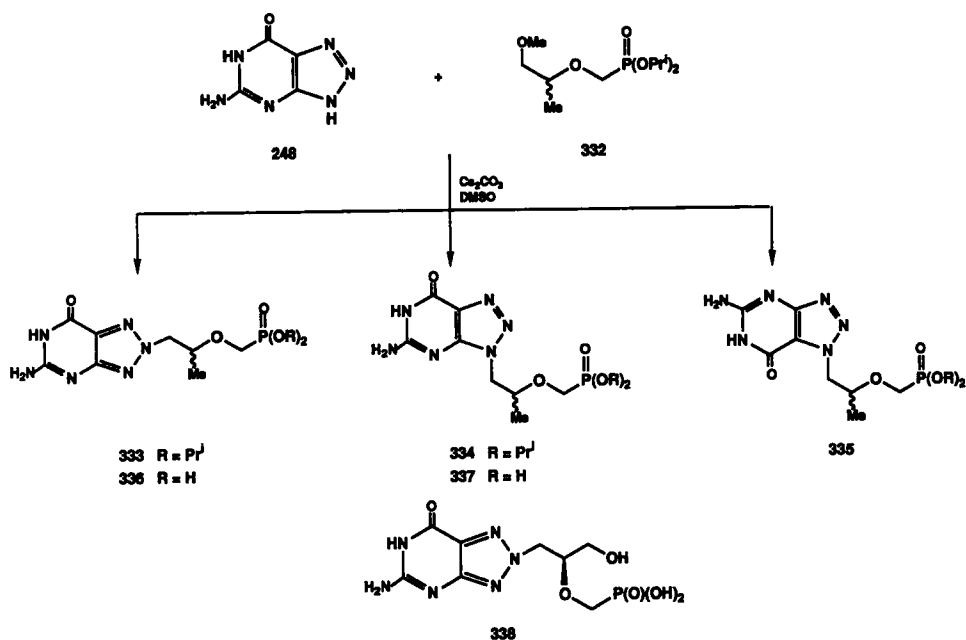


SCHEME 65

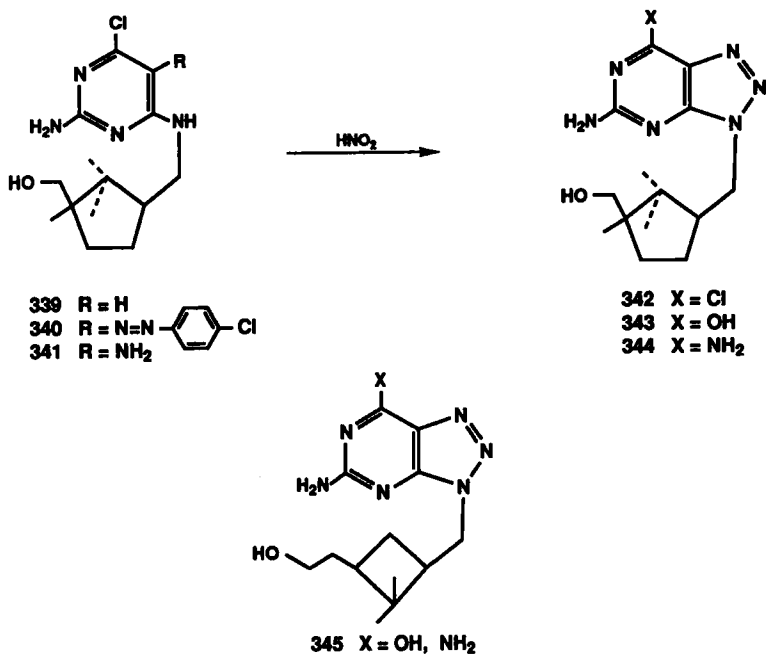
methyl]-1,2,2-trimethylcyclopentylmethanol (**342**). Basic hydrolysis of **342** with NaOH gave the 8-azaguanosine analog **343**, whereas treatment with ammonia gave the corresponding 2,6-diamino-8-azapurine analog **344** (95MI1). Several carbocyclic nucleosides **345** related to cyclobutane guanosine have been synthesized from pinonic acid (95MI2) (Scheme 67).

### BIOLOGICAL PROPERTIES

3-Phenyl-1,2,3-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one has bactericidal activity against *Bacillus subtilis* and *Staphylococcus aureus* (94MI2). 1-Benzyl-4-ethoxycarbonylpiperazinyl-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidine almost completely removed cytokinin-stimulated effects in betacyanin synthesis in *Amaranthus caudatus* cotyledons, growth of radish cotyledons, and retention of chlorophyll in leaf explants (94MI4). Analogs of **117** were used as effective inhibitors of xanthine oxidase (95FA257).



SCHEME 66



SCHEME 67

5-(4-Pyridinyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one **313** has been shown to be a potent competitive antagonist of the AMPA subtype glutamate receptor. It may be useful as a neuroprotectant (95JMC587).

The isopropylidene derivative of **318** generally improved affinity toward A<sub>1</sub> receptors. Its affinity with the corresponding 2-phenyl-9-benzyl-8-azaadenines confirmed the more complex arrangement of 8-azaadenines inside A<sub>1</sub> receptors, in which three lipophilic pockets are present. The selectivity of the N-6-substituted compound was higher than that of the N-6-unsubstituted compounds (95FA13).

The 5'-(phenylmethoxy)alaninyl phosphate derivative of **330** was found to be active against HIV-1 and HIV-2 with a potency similar to that of the 8-deaza analog and the 5'-triphosphate derivative of **330** was an active inhibitor of HIV-1 recombinant reverse transcriptase (94JMC3534). The (*R*) and (*S*)-8-aza-9-[(2-phosphonomethoxy)propyl]guanines [(*R*)- and (*S*)-8-aza-PMPG] (**337**) were tested *in vitro* for anti-HIV activity. The (*S*)-isomer was found to be less potent than its (*R*)-enantiomer (95JMC4007).

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## Some Recent Developments in Chalcogen Heterocyclic Chemistry

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*Dedicated to Prof. Dr. H.C. Margot-Becke, a pioneer in this field.*

I. Introduction .....	115
II. Preparation and Characterization of Small Heterocyclic Precursors .....	116
A. Bis(sulfinylamino)chalcogenanes $E(NSO)_2$ , $E = S, Se, Te$ .....	116
B. Perfluoroorganotellurocarbonyls $F(X)C=Te$ , $X = F, CF_3$ .....	118
III. Synthesis of Neutral and Ionic Heterocycles and Cages .....	119
A. Using $S(NSO)_2$ as a Precursor .....	119
B. Using $Se(NSO)_2$ as a Synthon .....	121
C. Using $Te(NSO)_2$ as a Starting Material .....	126
D. Using Previously Described Ditellura Heterocycles .....	130
E. Using $(CH_3)_3SiNSO$ and $[(CH_3)_3Si]_2N-E-N[Si(CH_3)_3]_2$ ( $E = S, Se$ ) as Precursors .....	132
F. Ditelluraetanes and Ditelluradiazetidines .....	134
IV. Discussion of and Support for Possible Reaction Pathways .....	136
V. Summary and Future Developments .....	142
References .....	143

### I. Introduction

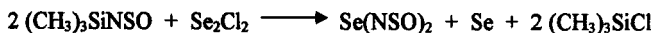
The objective of this chapter is to present evidence that simple noncyclic compounds such as  $E(NSO)_2$  ( $E = S, Se, Te$ ) and  $F(X)C=Te$  ( $X = F, CF_3$ ) can serve as synthons for the preparation of various heterocyclic rings and cages. In addition, reaction mechanisms will be postulated. Support for these pathways will be provided to allow a better understanding of the complicated processes that occur during ring or cage formation. Beginning with the preparation and characterization of the starting materials, the syntheses of a number of new and unexpected heterocyclic compounds and cage structures will be described. The different chemical reactions of  $E(NSO)_2$  ( $E = S, Se, Te$ ) that take place under similar conditions will be outlined and explained.

## II. Preparation and Characterization of Small Heterocyclic Precursors

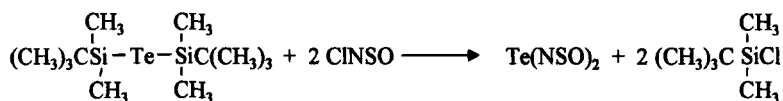
### A. BIS(SULFINYLAMINO)CHALCOGENANES E(NSO)<sub>2</sub> (E = S, Se, Te)

Bis(sulfinylamino)sulfane, first prepared by Goehring and Schuster (52AG617), is formed in a number of reactions starting from S<sub>4</sub>N<sub>4</sub> and NH<sub>4</sub>Cl or NH<sub>3</sub> and treating these materials with SOCl<sub>2</sub>, SO<sub>2</sub>, or S<sub>2</sub>Cl<sub>2</sub> (90MI1). The best methods to prepare S(NSO)<sub>2</sub> on a large scale are treatment of (CH<sub>3</sub>)<sub>3</sub>SiNSO with SCl<sub>2</sub> at reflux temperature (48 h) in a dry inert atmosphere (68% yield) (72IC1151) or reacting (CH<sub>3</sub>)<sub>3</sub>SiN=S=NSi(CH<sub>3</sub>)<sub>3</sub> with SOCl<sub>2</sub> in C<sub>6</sub>H<sub>6</sub> at 60°C (3 h, 83% yield) (75CB2340; 85BAU2571, 85IZV2774). Only one synthesis has been described for bis(sulfinylamino)selenane, prepared in good yields from pure (CH<sub>3</sub>)<sub>3</sub>SiNSO and Se<sub>2</sub>Cl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 22°C (24 h, 69%) (91CB1895) according to the stoichiometry shown in Scheme 1. New routes were needed for the synthesis of bis(sulfinylamino)tellurane as analogous reactions failed. It was found that [(CH<sub>3</sub>)<sub>3</sub>C(CH<sub>3</sub>)<sub>2</sub>Si]<sub>2</sub>Te reacts with ClNSO at 22°C (48 h, 36%) in CH<sub>2</sub>Cl<sub>2</sub> according to Scheme 2. The by-products are tellurium and S(NSO)<sub>2</sub>. This procedure is very time-consuming, and in 2 months only 2 g of pure Te(NSO)<sub>2</sub> were formed (89C261). New ways were explored, and it was found that bis(trifluoromethylthio)tellurium, Te(SCF<sub>3</sub>)<sub>2</sub>, is a synthon of high potential for the preparation of Te(NSO)<sub>2</sub>. However, Te(SCF<sub>3</sub>)<sub>2</sub> had only been obtained on a milligram scale by treating tellurium with CF<sub>3</sub>S radicals and was poorly characterized (83IC359). Improved yields (83%) and preparative amounts are obtained by treating a melt of Hg(SCF<sub>3</sub>)<sub>2</sub> with TeCl<sub>4</sub> for 1 h under dry argon.

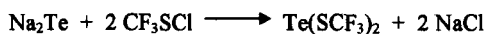
A simpler method is the reaction between CF<sub>3</sub>SCl and Na<sub>2</sub>Te in ether at 20°C (4 h, 50% yield). An almost quantitative reaction took place between [R<sub>3</sub>Sn]<sub>2</sub>Te (R = *n*-C<sub>4</sub>H<sub>9</sub>, C<sub>6</sub>H<sub>5</sub>) and CF<sub>3</sub>SCl at 20°C (4 h). The starting materials are made from Na<sub>2</sub>Te and Ph<sub>3</sub>SnCl or (*n*-C<sub>4</sub>H<sub>9</sub>)SnH plus Te. These reactions took place according to Scheme 3. When Te(SCF<sub>3</sub>)<sub>2</sub> and Hg(NSO)<sub>2</sub> are allowed to react at 50°C (5 days in the dark) a metathesis takes place between two parahalogenes (82CZ239; 84MI1; 91PAC1577), forming Te(NSO)<sub>2</sub> in 62% yield, Scheme 4. As the starting materials for this synthesis are now readily available, it is the best method for the preparation of any quantity of Te(NSO)<sub>2</sub> (95CB477). Structural parameters and some physical data for E(NSO)<sub>2</sub> are presented in Table I. The planar chainlike



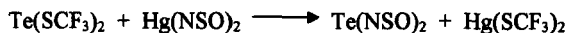
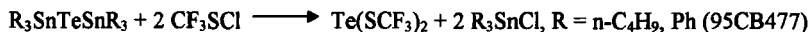
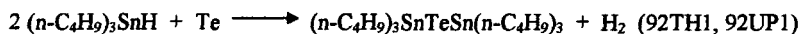
SCHEME 1



SCHEME 2



SCHEME 3



SCHEME 4

TABLE I  
PHYSICAL DATA AND STRUCTURAL PARAMETERS FOR E(NSO)<sub>2</sub>

	S(NSO) <sub>2</sub>	Se(NSO) <sub>2</sub>	Te(NSO) <sub>2</sub> (89C261)
color	yellow (90MI1)	yellow (91CB1895)	red
sublimation (°C/Torr)	25–30/10 <sup>-2</sup> (79CJC1286) 35/10 <sup>-2</sup> (53ZAAC297)	22/10 <sup>-3</sup> (87C340)	50/10 <sup>-3</sup>
m.p. (°C)	100.8 [67JCS(A)1437] 100.7 (53ZAAC297)	122–123 (91CB1895)	132 (decomp.)
d(E–N) <sup>a</sup> [Å]	1.647(3) (81CJC187)	1.827(5) (91CB1895)	2.039(7)
d(S–O) <sup>a</sup> [Å]	1.446(4) (81CJC187)	1.436(6) (91CB1895)	1.460(7)
d(S–N) <sup>a</sup> [Å]	1.535(3) (81CJC187)	1.516(6) (91CB1895)	1.492(7)
∠ <sup>b</sup> (N–E–N)	97.3(2)° (81CJC187)	92.0(2)° (91CB1895)	87.3(3)°
∠ <sup>b</sup> (N–S–O)	118.0(2)° (81CJC187)	117.9(3)° (91CB1895)	116.6(4)°
∠ <sup>b</sup> (E–N–S)	124.3(2)° (81CJC187)	123.2(3)° (91CB1895)	122.0(4)°

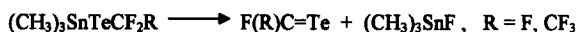
<sup>a</sup> Bond length.<sup>b</sup> Ditechal angle

molecules are sensitive to moisture, but solutions in completely dry solvents are stable.  $\text{S(NSO)}_2$  is soluble in benzene, nitrobenzene, heptane, petroleum ether, and alcohols (53ZAAC297).  $\text{Se(NSO)}_2$  is very soluble in  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , and acetone; moderately soluble in benzene, toluene, or liquid  $\text{SO}_2$ ; but almost insoluble in  $\text{CCl}_4$  and  $\text{CFCl}_3$  (91CB1895).  $\text{Te(NSO)}_2$  is only slightly soluble in  $\text{CH}_2\text{Cl}_2$  and  $\text{CS}_2$  and sparingly in  $\text{CH}_3\text{NO}_2$  (95CB477).

## B. PERFLUOROORGANOTELLUROCARBONYLS $\text{XFC}=\text{Te}$ ( $\text{X} = \text{F}, \text{CF}_3$ )

The successful preparation of the perfluorotellurocarbonyls provided an entirely new type of compound for the synthesis of various heterocycles. The first synthesis of difluorotellurocarbonyl, in about a 10% yield, employed the reaction of  $\text{Hg}(\text{TeCF}_3)_2$  and  $(\text{C}_2\text{H}_5)_2\text{ARI}$  without a solvent at  $20^\circ\text{C}/10^{-4}$  torr [93JSC(D)2547]. A better and more efficient method is pyrolysis at  $280^\circ\text{C}/10^{-3}$  torr of  $(\text{CH}_3)_3\text{SnTeCF}_3$ , which is prepared from  $(\text{CH}_3)_3\text{SnH}$  and  $\text{CF}_3\text{Te}_x\text{CF}_3$  ( $x = 1, 2$ ) in good yield, providing  $\text{CF}_2=\text{Te}$  in a 50 to 60% yield [93JSC(D)2547]. Similarly,  $\text{CF}_3(\text{F})\text{C}=\text{Te}$  is made from  $(\text{CH}_3)_3\text{SnTeCF}_2\text{CF}_3$  at  $500^\circ\text{C}/10^{-3}$  torr in 50 to 60% yield [96JCS(D)4463] according to Scheme 5. The highly reactive compounds  $\text{F(X)C}=\text{Te}$  ( $\text{X} = \text{F}, \text{CF}_3$ ) are characterized by chemical reactions forming heterocycles (see p. 134–135) and by IR and mass spectroscopy.

The IR spectrum of  $\text{F}_2\text{C}=\text{Te}$  obtained at  $10^{-3}$  torr in the gas phase shows only two bands,  $\nu_1$  and  $\nu_4$ , out of six theoretically possible vibrations with the expected fine structure. The A-type band  $\nu_1$  has absorptions at  $1244.4(\text{R})$ ,  $1240.0(\text{Q})$ , and  $1232.2\text{ cm}^{-1}(\text{P})$ , and the B-type band  $\nu_4$  has absorptions at  $1206.7(\text{R})$  and  $1195.4\text{ cm}^{-1}(\text{P})$ . These are assigned to  $\nu(\text{C}=\text{Te})$  and  $\nu_{\text{as}}(\text{CF}_2)$  and appear in the Amatrix spectrum at  $1226.0$  and  $1185.5\text{ cm}^{-1}$  [93JCS(D)2547]. The gas phase IR spectrum of  $\text{F}_3\text{C}(\text{F})\text{C}=\text{Te}$  shows bands at  $1284(\text{s})$ ,  $1224(\text{s})$ ,  $1166(\text{vs})$ ,  $1039(\text{w})$ ,  $968(\text{m})$ ,  $896(\text{w})$ , and  $736(\text{w})\text{ cm}^{-1}$ . Because of the loss of symmetry, no precise assignment has been made [96JCS(D)4463]. In the mass spectra of  $\text{F}_2\text{C}=\text{Te}$  [93JCS(D)2547] and  $\text{CF}_3(\text{F})\text{C}=\text{Te}$  [96JCS(D)4463], the molecular ion peak and the expected fragmentation pattern were observed. At the temperature of liquid nitrogen, solid  $\text{F}_2\text{C}=\text{Te}$  is violet [93JCS(D)2547] and  $\text{CF}_3(\text{F})\text{C}=\text{Te}$  is green [96JCS(D)4463].



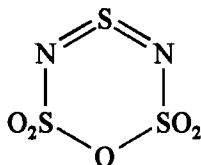
SCHEME 5

### III. Synthesis of Neutral and Ionic Heterocycles and Cages

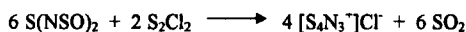
#### A. USING $S(NSO)_2$ AS A PRECURSOR

Inorganic binary sulfur–nitrogen heterocycles or cages were first prepared by treating  $S(NSO)_2$  with either  $TiCl_4$  or  $SbCl_5$ . The reaction of  $S(NSO)_2$  with  $TiCl_4$  in  $CH_2Cl_2$  yields a yellow precipitate, which was described as a 1 : 2 adduct of  $S_4N_4$  and  $TiCl_4$  with the formula  $S_4N_4 \cdot 2TiCl_4$  (65ZAAC126). A reinvestigation using IR and mass spectroscopy shows that the correct formula is  $S_2N_2 \cdot TiCl_4$ . The structure of this adduct should be a polymeric chain of alternating square planar  $S_2N_2$  rings. The reactions of  $S(NSO)_2$  with  $SnCl_4$  or  $SeCl_4$  under similar conditions do not give analogous  $S_2N_2$  adducts. The ultra-high-vacuum pyrolysis of  $S(NSO)_2$  at 200 to 400°C also fails to give  $S_2N_2$ . Only the starting materials are recovered (84IC75).

The reaction of  $S(NSO)_2$  with  $SbCl_5$  in  $CH_2Cl_2$  at 20°C gives red crystals of a compound with the formula  $S_4N_4 \cdot SbCl_5$  (65ZAAC126). Its structure was predicted to be an  $S_4N_4$  cage with  $SbCl_5$  coordinated at a nitrogen atom (60ACSA726). A 7-membered ionic heteroring is formed almost quantitatively on heating  $S(NSO)_2$  and  $S_2Cl_2$  in  $CH_3CN$  or  $CH_3NO_2$  according to Scheme 6. At room temperature after 10 minutes green-black crystals of  $(S_3N_2Cl)_2$  are deposited. On heating they are transformed to yellow  $[S_4N_3]Cl$ . Hydrolysis of  $S(NSO)_2$  with small amounts of water provides  $S_4N_4$  (53ZAAC297; 65ZAAC126). Aqueous NaOH causes rapid hydrolysis to  $(NH_4)_2S_3O_6$  (53ZAAC297). Ring formation is also observed when  $S(NSO)_2$  is treated with  $SO_3$  gas at 20°C. Initially, almost black  $S(NSO)_2 \cdot SO_3$  is obtained, and it slowly decomposes to  $S_3N_2O_5$  and  $SO_2$  [54ZN(B)678]. If  $S(NSO)_2$  is treated with liquid  $SO_3$ , a slightly exothermic reaction takes place, giving an 82% yield of  $S_3N_2O_5$ , which has the following ring structure (54ZAAC47):



Attempts to incorporate tellurium into S–N-containing heterocycles by using  $S(NSO)_2$  were also studied. The reaction between  $S(NSO)_2$  and  $TeCl_4$  at



SCHEME 6



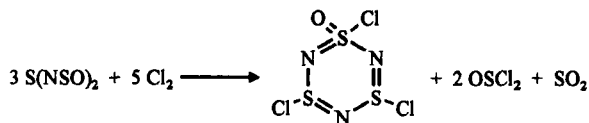
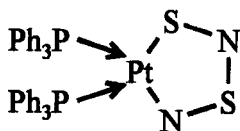
60°C in  $\text{CH}_2\text{Cl}_2$  for 4 weeks yields a crystalline mixture of red octahedra and yellow needles. These can be separated manually in a glove box fitted with a polarization microscope. The red crystals are identified as  $\text{S}_4\text{N}_4 \cdot \text{TeCl}_4$  (78JINC203). The yellow needles prove to be  $[\text{S}_5\text{N}_5^+][\text{Te}_3\text{Cl}_{13}^-]$ , a heart-shaped 14- $\pi$ -electron pentathiopentazocinium cation. Incorporation of tellurium in a chalcogen-nitrogen system is not observed.  $[\text{S}_5\text{N}_5^+][\text{Te}_3\text{Cl}_{13}^-]$  is characterized by X-ray crystallography and consists of discrete  $\text{S}_5\text{N}_5^+$  and  $\text{Te}_3\text{Cl}_{13}^-$  ions (95CB11). Oxidative chlorination of  $\text{S}(\text{NSO})_2$  is another way to prepare heterocycles containing S-N moieties. Treatment with liquid  $\text{Cl}_2$  at  $-80^\circ\text{C}$  and subsequent warming to  $20^\circ\text{C}$  yields almost white crystals of trithiazyltrichlorideoxide as well as  $\text{SO}_2$  and  $\text{OSCl}_2$  (68ZAAC1) according to Scheme 7.

When this chlorination process was repeated two minor products,  $[\text{NS}(\text{O})\text{Cl}]_2(\text{NSCl})$  and  $[\text{NS}(\text{O})\text{Cl}]_3$ , were isolated by careful sublimation [76JINC(S)213]. Sulfuryl dichloride reacts with  $\text{S}(\text{NSO})_2$  at  $20^\circ\text{C}$  (24 h) forming 83%  $[\text{ClS}(\text{O})\text{N}](\text{NSCl})_2$ , which is transformed at  $70^\circ\text{C}$  (5 days) in 26% yield according to Scheme 8.

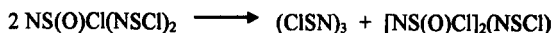
X-ray structure determination on single crystals of  $[\text{NS}(\text{O})\text{Cl}]_n$  ( $\text{ClSN})_{3-n}$ ,  $n = 1, 2$ , shows that both compounds have structures similar to trithiazyltrichloridetrioxide and trithiazyltrichloride. Structural parameters for  $[\text{ClS}(\text{O})\text{N}]_n(\text{NSCl})_{3-n}$  ( $n = 0, 1, 2, 3$ ) are summarized and discussed [93ZN(B)901].

Using  $\text{PCl}_5$  as a chlorinating agent, 1,3,3,5,5-pentachloro-1 $\lambda^4$ ,2,4,6,3 $\lambda^5$ ,5 $\lambda^5$ -thiatriazadiphosphorin is formed at 35 to  $38^\circ\text{C}$  (2–3 h) [72AG685, 72AG(E)642].

Metallaheterocycles are also obtained using  $\text{S}(\text{NSO})_2$ . Reacting  $(\text{Ph}_3\text{P})_2\text{PtCH}_2=\text{CH}_2$  with  $\text{S}(\text{NSO})_2$  at  $20^\circ\text{C}$  (15 min) in toluene gives 64%  $(\text{Ph}_3\text{P})_2\text{PtS}_2\text{N}_2$  as bright yellow crystals with the following structure (86ICA145).



SCHEME 7



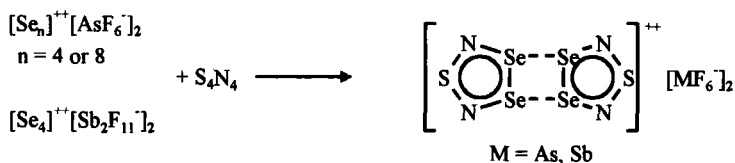
SCHEME 8

### B. USING $\text{Se(NSO)}_2$ AS A SYNTHON

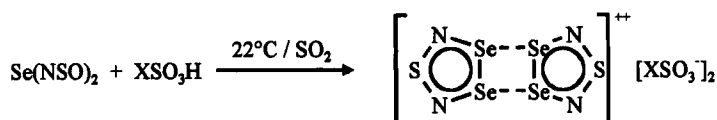
Very surprisingly  $\text{Se(NSO)}_2$  proves to be an excellent precursor for the preparation of seleno- and tellurasulfur-nitrogen ring systems: It reacts with Lewis acids such as  $\text{MF}_5$  ( $\text{M} = \text{As}, \text{Sb}, \text{Nb}$ ) and  $\text{BF}_3$  in liquid  $\text{SO}_2$  at room temperature to yield bis(1,3,4,2,5-thiadiselenadiazolium) cations with the counteranions  $\text{AsF}_6^-$ ,  $\text{SbF}_6^-$ ,  $\text{NbF}_6^-$  and  $\text{BF}_4^-$  (91CB1895). The first two compounds were synthesized initially by Gillespie *et al.* (81IC4053) by reacting  $[\text{Se}_n]^{++}[\text{AsF}_6^-]_2$  ( $n = 4$  or  $8$ ) or  $[\text{Se}_4]^{++}[\text{Sb}_2\text{F}_{11}^-]_2$  with  $\text{S}_4\text{N}_4$  in liquid  $\text{SO}_2$  at  $22^\circ\text{C}$  (see Scheme 9).

The structure of the dication consists of two planar  $\text{Se}_2\text{N}_2\text{S}$  5-membered rings linked by two weak  $\text{Se} \cdots \text{Se}$  interactions in a chair conformation. Strong Brönsted acids such as  $\text{CF}_3\text{SO}_3\text{H}$  or  $\text{FSO}_3\text{H}$  react with  $\text{Se(NSO)}_2$  under similar conditions, forming the dication (see Scheme 10). The structure of the dication is almost identical with that published previously (81IC4053). The bond lengths and angles do not differ significantly. Molecular parameters are listed in Table II (92CB789). Using  $\text{Se(NSO)}_2$  as a starting material the dication is readily prepared and could be used for further investigations. In  $\text{SO}_2$  solution it dissociates to the radical cation  $\text{Se}_2\text{N}_2\text{S}^{\cdot+}$ , which is detected by ESR spectroscopy and shows a quintet with a coupling constant of 3.0 gauss. The 5-membered ring has a planar structure with a delocalized  $\pi$ -electron system with two equivalent nitrogen atoms. On reaction with halogens the dication forms 3-halogeno-1,3,4,2,5-thiadiselenadiazolium cations in almost quantitative yield (see Scheme 11). X-ray structure investigations show that the new compounds are ionic, having a planar 5-membered ring with an exocyclic halogen bonded to selenium and a distorted octahedral anion. It was not possible to obtain the corresponding iodo derivatives using the synthons described in Scheme 11.

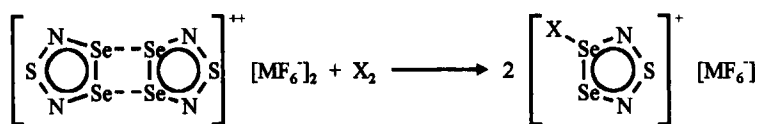
A different behavior is observed in the reaction of  $\text{Se(NSO)}_2$  with  $\text{PCl}_5$ ,  $\text{SeCl}_4$ , or  $\text{POCl}_3$ . With  $\text{PCl}_5$  and  $\text{SeCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at  $22^\circ\text{C}$  (8 or 22 days) crys-



SCHEME 9



SCHEME 10



M = As, X = Cl, Br; M = Nb, X = Cl

SCHEME 11

TABLE II  
STRUCTURAL PARAMETERS FOR THE FIVE-MEMBERED RING OF  $[\text{SeSeNSN}]_2^{++}[\text{A}^-]_2$ ,  
 $[\text{ClSeSeNSN}]^+[\text{B}^-]$ , and  $\text{Cl}_2\text{SeSeNSN}$  (DISTANCES IN Å, ANGLES IN DEGREES)

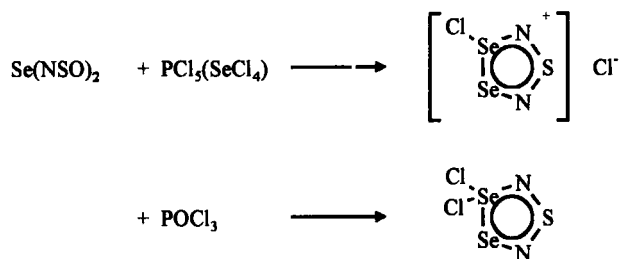
	[A <sup>-</sup> ]		[B <sup>-</sup> ]			
	[AsF <sub>6</sub> <sup>-</sup> ] <sup>a</sup> (81IC4053)	[CF <sub>3</sub> SO <sub>3</sub> <sup>-</sup> ] <sup>b</sup> (92CB789)	[NbF <sub>6</sub> <sup>-</sup> ] (91CB1895)	[SbCl <sub>6</sub> <sup>-</sup> ] (91CB1895)	[Cl <sup>-</sup> ] (91CB1895)	Cl <sub>2</sub> SeSeNSN (91CB1895)
d(Se-1-Se-2)	2.358	2.363(1)	2.377(2)	2.359(2)	2.415(1)	2.384(2)
d(Se-1-N-2)	1.75	1.789(4)	1.760(9)	2.02(2)	1.813(3)	1.771(9)
d(Se-2-N-1)	1.75	1.786(4)	1.77(1)	1.80(2)	1.820(2)	1.78(1)
d(S-N-1)	1.57	1.552(5)	1.53(1)	1.49(2)	1.545(3)	1.54(1)
d(S-N-2)	1.55	1.560(5)	1.594(9)	1.46(2)	1.578(3)	1.584(9)
d(Se-1-Cl)	—	—	2.211(3)	2.188(3)	2.265(1)	2.353(3)
d(Se-1-Cl <sup>-</sup> )	—	—	—	—	2.825(1)	2.644(3)
∠(Se-1-Se-2-N-1)		93.8(1)	92.4(3)	93.6(5)	91.7(1)	93.0(3)
∠(Se-2-Se-1-N-2)		93.8(2)	94.1(3)	81.1(4)	94.9(1)	94.4(3)
∠(N-1-S-N-2)		113.2(2)	111.9(5)	107.6(9)	114.8(1)	113.5(5)
∠(Se-1-N-2-S)		119.5(3)	118.8(5)	113.4(9)	117.2(2)	118.6(5)
∠(Se-2-N-1-S)		119.6(3)	121.7(6)	120(1)	120.8(2)	120.3(6)
∠(Cl-1-Se-1-Cl-2)	—	—	—	—	174.3(1)	164.9(1)
∠(Cl-2-Se-1-Se-2)	—	—	101.9(1)	106.1(1)	98.8(1)	92.5(1)
∠(Cl-1-Se-2-N-2)	—	—	102.6(3)	115.1(5)	87.6(1)	95.6(3)

<sup>a</sup> d(Se-2a...Se-1b) = 3.159; d(Se-1a...Se-2b) = 3.111

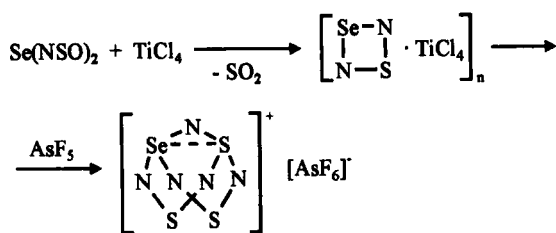
<sup>b</sup> d(Se-2a...Se-1b) = 3.084; d(Se-1a...Se-2b) = 3.084

tals are formed, whereas  $\text{POCl}_3$  reacts without a solvent at  $50^\circ\text{C}$  (8 days), yielding orange-red crystals (see Scheme 12). In the first case the two products are identical and characterized as ionic  $[\text{ClSeSeNSN}]\text{Cl}$  by an X-ray analysis. The second product has the same stoichiometric formula but in some areas distinctly different IR absorptions. The X-ray crystal structure shows remarkable deviations for the  $(\text{SeI}-\text{Cl})$  and  $(\text{SeI}-\text{Cl}^-)$  distances from those of the ionic species (see Table II). This significant difference, 2.644(3), 2.351(3) Å compared to 2.825(1), 2.265(1) Å, is rationalized by more covalent bonding of the two chlorine atoms to selenium. A completely different type of compound is obtained by treating  $\text{Se}(\text{NSO})_2$  with  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at  $22^\circ\text{C}$  (24 h), forming  $\text{SeSN}_2 \cdot \text{TiCl}_4$  and  $\text{SO}_2$  in almost quantitative yields. A study of the orange-yellow product in terms of its thermal stability, solubility and IR spectrum below  $500\text{ cm}^{-1}$  shows it to be polymeric 1,3,2,4- $\text{SeSN}_2 \cdot \text{TiCl}_4$  (84IC75). In the X-ray powder analysis both materials 6- $\text{S}_2\text{N}_2 \cdot \text{Tilly}$  and  $\text{SeSN}_2 \cdot \text{Tilly}$  are isostructural. Attempts to replace  $\text{TiCl}_4$  by another Lewis acid such as  $\text{AsF}_5$  in  $\text{SO}_2$  at  $22^\circ\text{C}$  (24 h) yield bright yellow crystals of  $3\lambda^4, 5\lambda^4, 7\lambda^4$ -trithia-1 $\lambda^4$ -seleno-2,4,6,8-tetraza-9-azoniabicyclo [3.3.1]-1(9),2,3,5(9),6,7-hexane hexafluoroarsenate. The X-ray determination reveals an ionic cage structure comparable to that of  $[\text{S}_4\text{N}_5]^+$  [78JCS(CC)212; 79IC3379; 82ZN(B)1388], with the selenium atom bonded to the bridging  $\text{N}^+$  atom (see Scheme 13). This was the first synthesis of an ion having a sulfur atom in  $\text{S}_4\text{N}_5^+$  replaced by selenium.

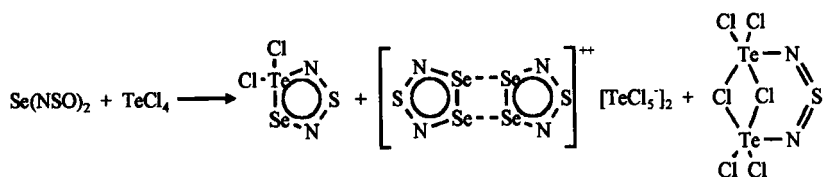
Bis(sulfinylamino)selane is also a good starting material for the preparation of tellura chalcogena-nitrogen heterocycles. In a lengthy reaction with  $\text{TeCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at  $22^\circ\text{C}$  (28 days) red crystals of 3,3-dichloro-1,3 $\lambda^4$ ,4,2,5-thiatelluraselena-diazol are formed; they are separated mechanically (92CB789). When this procedure is carried out at  $60^\circ\text{C}$  (28 days), a mixture of products is obtained (see Scheme 14). Using a microscope in a dry argon atmosphere it is possible to separate three compounds, the previously mentioned  $\text{Cl}_2\text{TeSeNSN}$ , bis(1,3,4,2,5-thiadiselenadiazolium) bis(pentachlorotellurate), and di- $\eta$ -chloro-tetrachloro-1 $k^2\text{Cl}$ ,2 $k^2\text{Cl}$ - $\eta$ -sulfurdiimidato



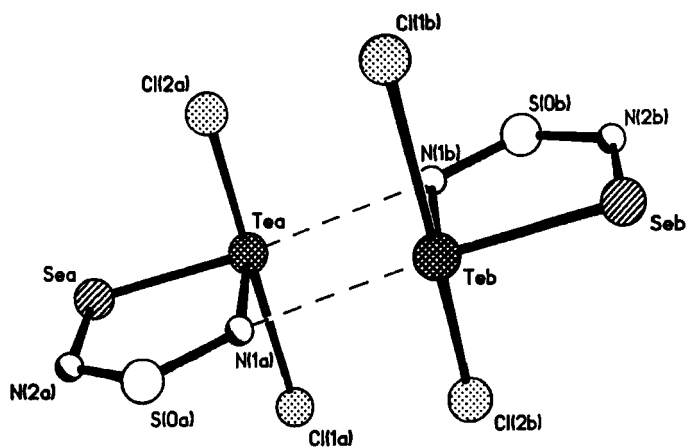
SCHEME 12



SCHEME 13



SCHEME 14

FIG 1. Molecular structure of  $\overline{\text{Cl}_2\text{TeSeNSN}}$ .

(2-)-1*kN*,2*kN'*-ditellurium. A dimeric unit of the crystal structure of  $\text{Cl}_2\text{TeSeNSN}$  are shown in Fig. 1 and a section of the crystal structure of  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  including the intermolecular contacts  $\text{Cl}(2) \cdots \text{Te}$  and  $\text{S} \cdots \text{Te}$  in Fig. 2. The  $\text{Cl}(2) \cdots \text{Te}$  (3.786 Å) and  $\text{S} \cdots \text{Te}$  (3.914 Å) distances are only slightly shorter than the sum of the Cl-Te and S-Te van der Waals radii and indicate no element-to-element bonding interactions. The procedure can be shortened by using  $[\text{TeCl}_3^+][\text{AsF}_6^-]$  instead of  $\text{TeCl}_4$  and  $\text{SO}_2$  as the solvent. Both starting materials are soluble in  $\text{SO}_2$ . After 1 h in a homogenous reaction (molar ratio 1 : 1) crystals of  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  form, and after 72 h formation of  $[\text{Se}_2\text{N}_2\text{S}^+]_2[\text{AsF}_6^-]_2$  is observed. After 7 days a mixture is iso-

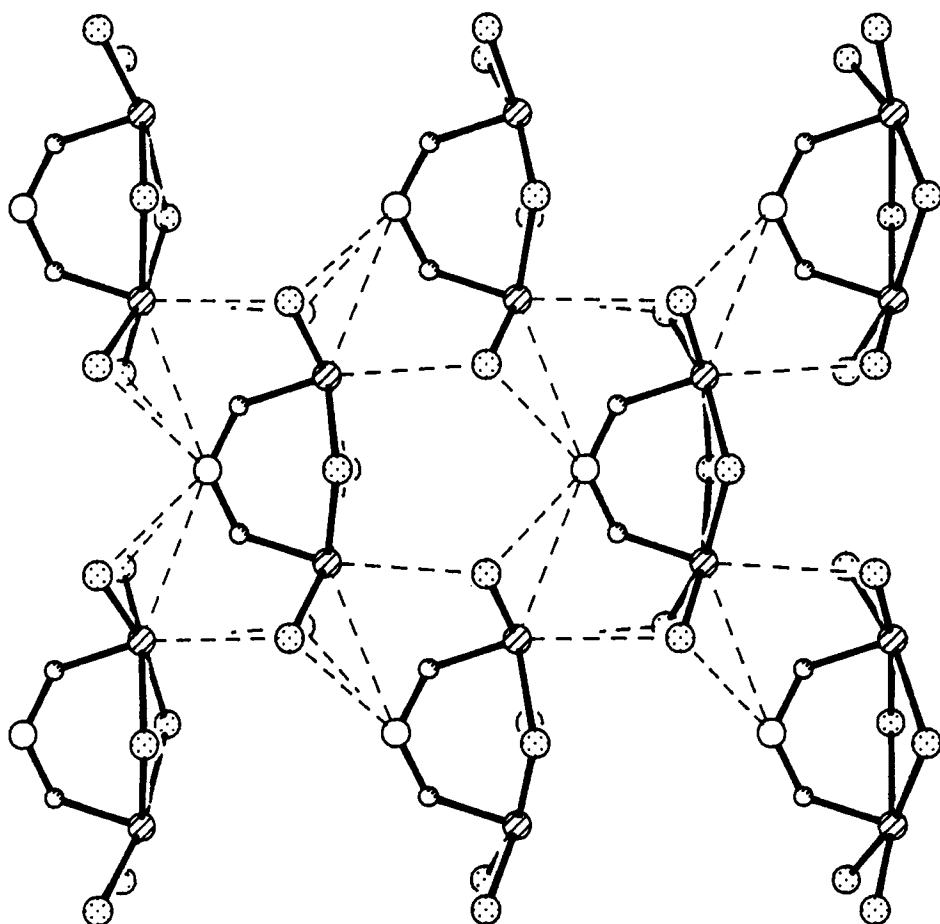
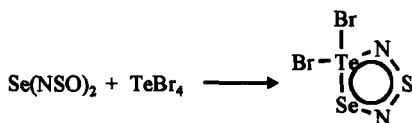


FIG. 2. A section of the crystal structure of  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  with intermolecular contacts between  $\text{Cl}(2) \cdots \text{Te}$  and  $\text{Te} \cdots \text{S}$ .



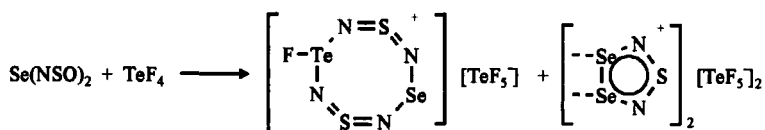
SCHEME 15

lated, dried, and separated mechanically. The reaction between  $\text{TeCl}_4$  and  $(\text{CH}_3)_3\text{SiNSO}$  in  $\text{CH}_2\text{Cl}_2$  at  $22^\circ\text{C}$  (12 h) is a better synthesis of  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$ , giving a yield of 95% (92CB1537). Less reactive  $\text{TeBr}_4$  and  $\text{Se(NSO)}_2$  in  $\text{CH}_2\text{Cl}_2$  at  $60\text{--}70^\circ\text{C}$  give, after 6 months, 70% 3,3-dibromo-1,3 $\lambda^4$ ,4,2,5-thi-atelluraselenadiazol and  $\text{SO}_2$  (see Scheme 15). No other products can be detected. A different type of compound is formed in the reaction of  $\text{TeF}_4$  and  $\text{Se(NSO)}_2$  at  $60^\circ\text{C}$  (7 days) in  $\text{CH}_2\text{Cl}_2$ , from which an almost quantitative yield of 7-fluoro-1 $\lambda^4\delta^4$ ,5 $\lambda^4\delta^2$ ,3, 7 $\lambda^3$ ,2,4,6,8-dithiaselenatelluratetrazocinium pentafluorotellurate and  $[\text{Se}_2\text{N}_2\text{S}^+]_2[\text{TeF}_5^-]_2$  are obtained along with  $\text{SO}_2$  (see Scheme 16).

The X-ray structure and cation-anion interaction in the crystal lattice are shown in Fig. 3. The X-ray analysis of the first molecule shows an 8-membered ring with fluorine bonded to the tellurium atom, which probably carries most of the positive charge. The anion  $[\text{TeF}_5^-]$  has a distorted square-pyramidal environment. Due to a short Te-Se distance (2.902 Å), the structure represents a partially opened three-dimensional cage similar to that in  $\text{S}_4\text{N}_4\text{Cl}_2$  [81AX(B)23]. In the lattice the molecule is stabilized by strong  $\text{Te} \cdots \text{F}$  (2.687 Å),  $\text{Se} \cdots \text{F}$  (2.952 Å), and  $\text{Te-1} \cdots \text{Te-2}$  (4.185 Å) cation-anion interactions (95CB11).

### C. USING $\text{Te(NSO)}_2$ AS A STARTING MATERIAL

Although  $\text{Te(NSO)}_2$  is now readily available on a preparative scale, it is not as useful as  $\text{Se(NSO)}_2$  for the preparation of the corresponding heterocycles. Its low thermal stability and extreme sensitivity to air and moisture limit its use as a synthon. The first 5-membered ring containing tellurium, sulfur, and nitrogen heteroatoms was made from  $\text{Te(NSO)}_2$  and  $\text{SbCl}_5$  (molecular ratio 2.1 : 1.5) in absolute  $\text{CH}_2\text{Cl}_2$  at  $-80^\circ\text{C}$  (12 h). The formation of  $\text{SO}_2$  as well as a yellow solid (not unambiguously characterized,



SCHEME 16

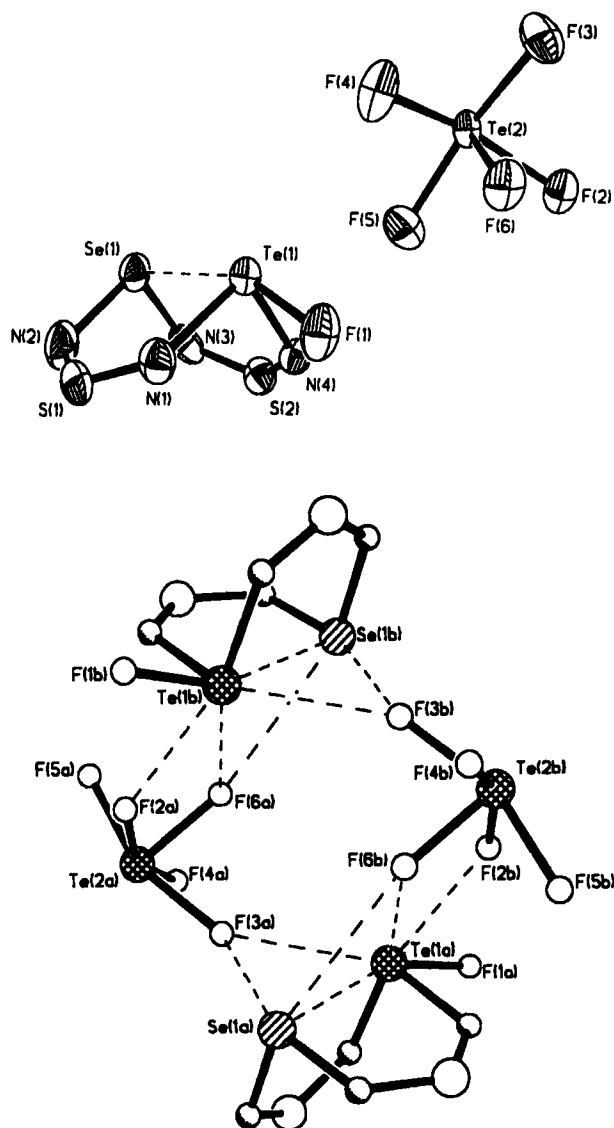
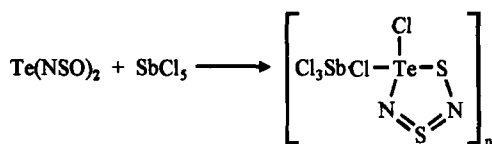


FIG 3. Crystal structure of  $[\text{FTeNSNSeNSN}^+][\text{TeF}_4^-]$  and cation-anion interaction in the crystal lattice.

probably a mixture of  $\text{TeCl}_4$  and  $\text{SbCl}_3$ ) and an orange-yellow colored liquid phase is observed. After filtration and washing the precipitate with  $\text{CH}_2\text{Cl}_2$ , the combined filtrates were concentrated to half of their volume *in vacuo*. After a few weeks yellow, cubic-shaped crystals are formed in about 1% yield (see Scheme 17).





SCHEME 17

An X-ray structure proves that the molecule is polymeric, consisting of 5-membered ring units having one chlorine bonded to tellurium and a second chlorine linking Te and Sb, probably through a three-center bond. The antimony is sixfold coordinated by Cl atoms. Three of these are almost equidistant [ $d(\text{Sb}-\text{Cl}) = 2.335\text{--}2.363 \text{ \AA}$ ] from Sb, indicating that Sb has the oxidation state III. The others are at a unique but greater distance [ $d(\text{Sb}-\text{Cl}) = 3.256\text{--}3.991 \text{ \AA}$ ] and bridge the tellurium and antimony. The frame of the polymer is constructed of two 4-membered rings containing  $\text{Sb}_2\text{Cl}_2$  and  $\text{Te}_2\text{Cl}_2$  units, with the following bond angles:  $\text{Sb}-\text{Cl}-\text{Sb} = 79.5^\circ$ ;  $\text{Cl}-\text{Sb}-\text{Cl} = 100.5^\circ$ ;  $\text{Cl}-\text{Te}-\text{Cl} = 85.2^\circ$ ;  $\text{Te}-\text{Cl}-\text{Te} = 94.8^\circ$ . The alternating rings are perpendicular to each other. Crystal structures of a single unit and a stereoscopic view of the crystal are shown in Fig. 4 (92MI1).

To understand this complicated reaction pathway, the intermediate  $\text{Cl}_2\text{Te}(\text{NSO})_2$  was postulated and then synthesized. Several methods have been used for its successful preparation. It was first made from  $\text{TeCl}_4$  and a mixture of  $(\text{CH}_3)_3\text{SiNSO}-[(\text{CH}_3)_3\text{Si}]_2\text{O}$  (1:2) containing 2 moles of  $(\text{CH}_3)_3\text{SiNSO}$  (relative to  $\text{TeCl}_4$ ) at  $20^\circ\text{C}$  (12 h) in a 10% yield (95CB11). Almost quantitative yields are obtained when  $\text{TeCl}_4$  reacts with 2 moles of  $(\text{CH}_3)_3\text{SiNSO}$  in  $\text{CH}_2\text{Cl}_2$  at  $-15^\circ\text{C}$  (5 h) (96TH1, 96UP1). Other convenient methods are chlorination of  $\text{Te}(\text{NSO})_2$  in a sealed tube at  $0^\circ\text{C}$  by allowing  $\text{Cl}_2$  to diffuse from the gaseous into the liquid phase, treating  $\text{Te}(\text{SCF}_3)_2$  with  $\text{ClNSO}$  at  $-78^\circ\text{C}$  (12 h), or reacting Te with  $\text{ClNSO}$  at  $0^\circ\text{C}$  (48 h) in  $\text{CS}_2$ , giving almost quantitative yields (95CB477). The corresponding  $\text{F}_2\text{Te}(\text{NSO})_2$  is made from  $\text{TeF}_4$  and  $(\text{CH}_3)_3\text{SiNSO}$  at  $20^\circ\text{C}$  (1 h) in 80% yield (95CB11). Both  $\text{Te}(\text{NSO})_2$  and  $\text{Cl}_2\text{Te}(\text{NSO})_2$  react with stoichiometric amounts of chlorine in  $\text{CS}_2$  at  $20^\circ\text{C}$  (12 h) (see Scheme 18), forming  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  with yields of 95% and 84% respectively (95CB477). Halogenation of  $\text{Cl}_2\text{Te}(\text{NSO})_2$  can also be accomplished by using reagents such as  $\text{CF}_3\text{SCl}$ ,  $\text{TeCl}_4$ , and  $\text{TeBr}_4$ . In the first case  $\text{Cl}_2\text{Te}(\text{NSO})_2$  reacts with  $\text{CF}_3\text{SCl}$  in  $\text{CH}_2\text{Cl}_2$  at  $-10^\circ\text{C}$  (3 days), forming  $\text{CF}_3\text{SNSO}$  and  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  in 95% yield. Similarly,  $\text{TeCl}_4$  and  $\text{TeBr}_4$  react with  $\text{Cl}_2\text{Te}(\text{NSO})_2$  in  $\text{CH}_2\text{Cl}_2$  at  $40^\circ\text{C}$  (12 h) to give  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  and  $\text{Cl}_2\text{Br}_4\text{Te}_2\text{N}_2\text{S}$  in yields of 96% and 92% (see Scheme 19). The reactions with  $\text{GaCl}_3$  and  $\text{GeCl}_4$  show that  $\text{Cl}_2\text{Te}(\text{NSO})_2$  is a very versatile synthon. It reacts rapidly with  $\text{GaCl}_3$  at  $0^\circ\text{C}$  forming the ionic product  $[\text{TeNSN}^{++}][\text{GaCl}_4^-]_2$  in an 80% yield and with

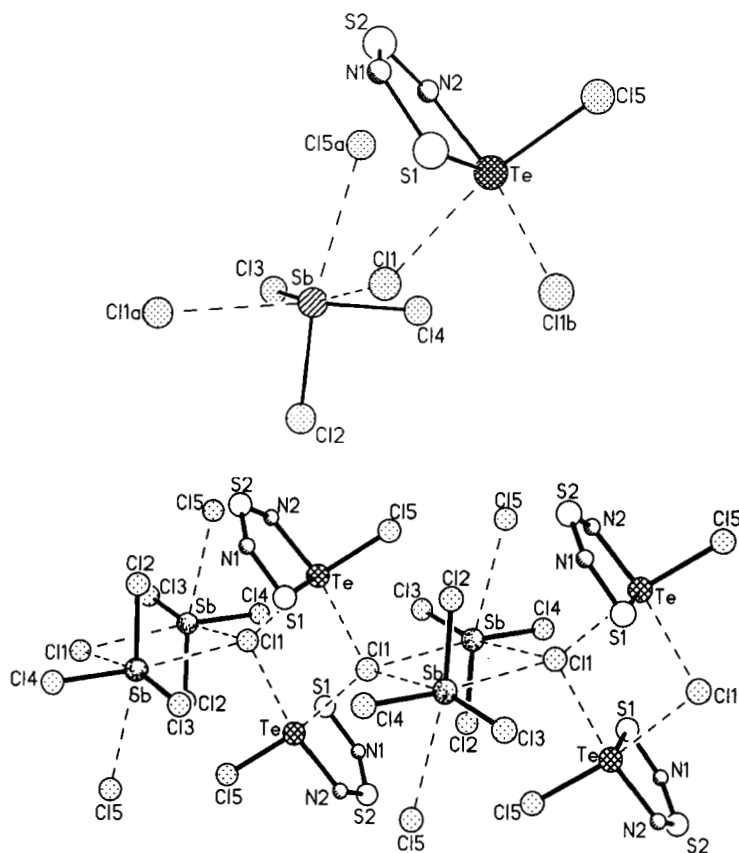
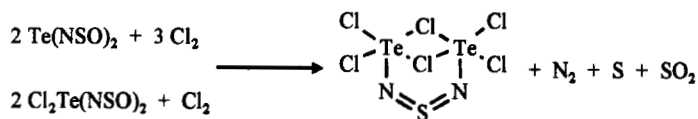
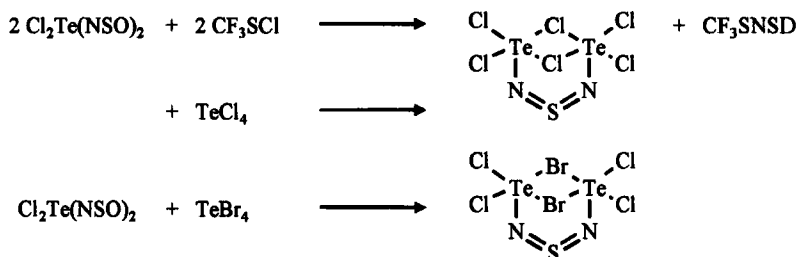


FIG 4. Crystal structure of a single unit of  $[\text{Cl}_3\text{Sb} \cdots \text{Cl} \cdots (\text{Cl})\text{TeSNSN}]_n$  and stereoscopic view of the crystal.

$\text{GeCl}_4$  at  $50^\circ\text{C}$  (3 days) in  $\text{CH}_2\text{Cl}_2$ , giving a yield of 95%  $\text{Cl}_2 \overline{\text{TeNSN}}$ . The latter is also formed from  $\text{Cl}_2\text{Te}(\text{NSO})_2$  and catalytic amounts of  $\text{CF}_3\text{SCl}$  at  $22^\circ\text{C}$  (12 h) in  $\text{CH}_2\text{Cl}_2$  in 95% yield, together with  $\text{CF}_3\text{SSCF}_3$  and  $\text{SO}_2$  (96TH1, 96UP1), (see Scheme 20). Both structures are not proven by an x-ray or analyses.



SCHEME 18



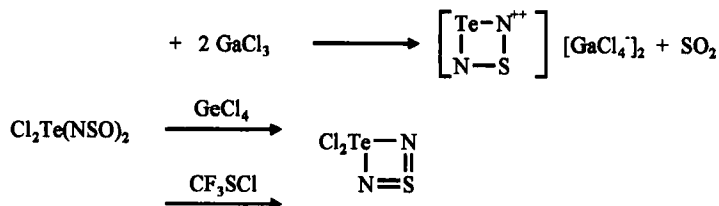
SCHEME 19

#### D. USING PREVIOUSLY DESCRIBED DITELLURA HETEROCYCLES

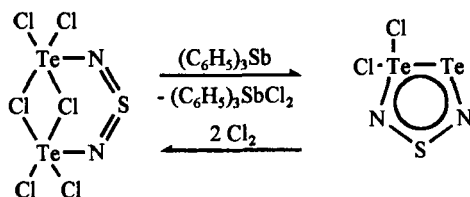
The high-yield synthesis of  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  allowed access to further interesting telluraheterocycles. The bicyclic  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  is dechlorinated with  $(\text{C}_6\text{H}_5)_3\text{Sb}$  to produce the 5-membered ring  $\text{Cl}_2\text{TeTeNSN}$  [92JCS(CC) 1144; 95CB11]. This reaction can be reversed by chlorination of  $\text{Cl}_2\text{TeTeNSN}$  with  $\text{Cl}_2$  [94JCS(CC)391] (see Scheme 21).

A different novel ditelluraheterocycle is obtained either by treating  $\text{Cl}_2\text{TeTeNSN}$  with  $\text{AsF}_5$  at  $22^\circ\text{C}$  (24 h) in  $\text{SO}_2$  (molar ratio 2:3) [92JCS(CC)1144; 95CB11] or with  $\text{Ag}[\text{AsF}_6]$  at  $22^\circ\text{C}$  (12 h stirring), forming  $[\text{ClTeTeNSN}^+][\text{AsF}_6^-]$  in about 80% yield (see Scheme 22). Single crystals are isolated from  $\text{SO}_2$  solution, and the X-ray structure confirms a cationic planar 5-membered ring with a short Te-Te (2.731 Å) and two short Te-N (2.009 and 2.020 Å) single-bond lengths as expected for a delocalized cationic ring. The cation-ion interactions are negligible [92 JCS(CC)1144; 95CB11]. This compound is a valuable starting material for the synthesis of other tellura heterocycles.

A different novel cage is prepared by treating  $\text{Cl}_2\text{TeTeNSN}$  with a three-fold excess of  $\text{AsF}_5$  in  $\text{SO}_2$  at  $22^\circ\text{C}$  (12 h), giving a 58% yield of a dithiaditelluratetrazocinium dication (see Scheme 22). The structure as elucidated by X-ray crystallography is an 8-membered ring with a Te-Te (2.881 Å)



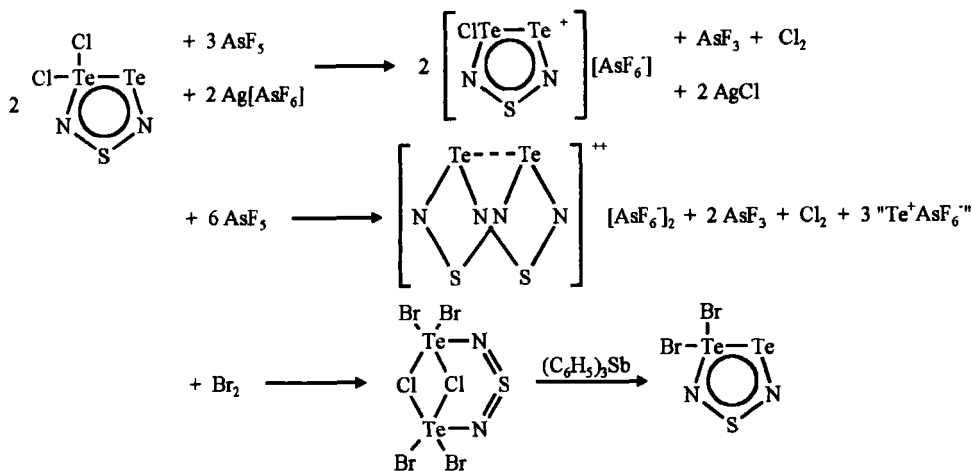
SCHEME 20



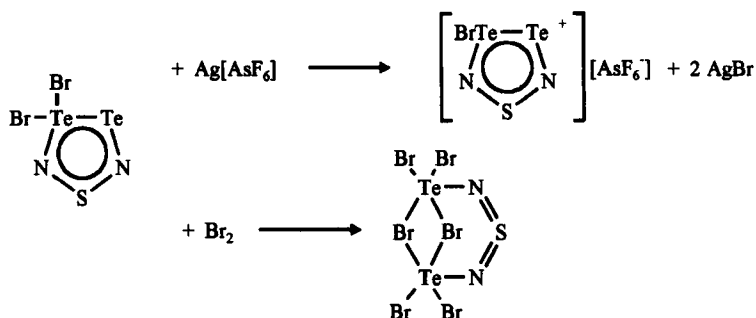
SCHEME 21

bridging bond. The three coordinated tellurium atoms, probably carrying most of the positive charge, are in a pyramidal environment. No secondary S-S bonding is detected, so the structure represents a partially opened three-dimensional cage [94JCS(CC)391; 95CB11].

The reaction of bromine with  $\text{Cl}_2\text{TeTeNSN}$ , on warming from  $-196^\circ\text{C}$  to room temperature in  $\text{CH}_2\text{Cl}_2$ , yields tetrabromo- $1k^2\text{Br}, 2k^2\text{Br}$ -di- $\mu$ -chloro- $\mu$ -[sulfurdiimidato(2-)- $1kN, 2kN'$ ]-ditellurium(IV) (see Scheme 22), which can be dehalogenated with  $(\text{C}_6\text{H}_5)_3\text{Sb}$  at  $22^\circ\text{C}$  (12 h) in  $\text{CH}_2\text{Cl}_2$ , giving  $\text{Br}_2\text{TeTeNSN}$  in 95% yield and  $(\text{C}_6\text{H}_5)_3\text{SbX}_2$  ( $\text{X} = \text{Cl}, \text{Br}$ ) (see Scheme 22). The dibromoheterocycle  $\text{Br}_2\text{TeTeNSN}$  also acts as a good synthon. It reacts with  $\text{Ag}[\text{AsF}_6]$ , giving  $[\text{BrTeTeNSN}^+][\text{AsF}_6^-]$ , and with bromine to form  $\text{Br}_6\text{Te}_2\text{N}_2\text{S}$  (see Scheme 23) [94JCS(CC)391; 95CB11]. Another novel ditellura heterocycle is prepared by treating  $\text{Cl}_6\text{Te}_2\text{N}_2\text{S}$  with  $(\text{CH}_3)_3\text{SiN}=\text{S}=\text{NSi}(\text{CH}_3)_3$  at  $22^\circ\text{C}$  (2 days) in  $\text{CH}_2\text{Cl}_2$  yielding the 8-membered ring  $\text{Cl}_2\text{Te}(\text{N}=\text{S}=\text{N})_2\text{TeCl}_2$  (see Scheme 24) [94JCS(CC)391; 95CB1].



SCHEME 22

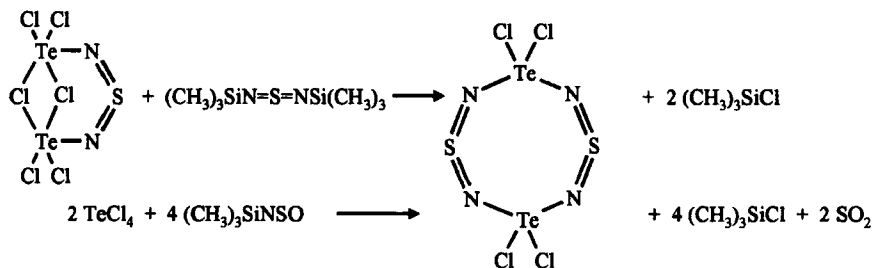


SCHEME 23

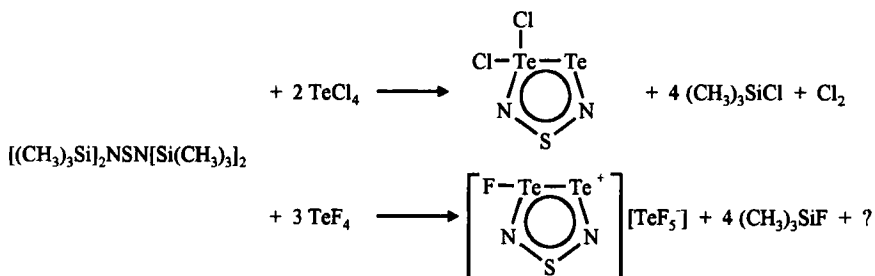
E. USING  $(\text{CH}_3)_3\text{SiNSO}$  AND  $[(\text{CH}_3)_3\text{Si}]_2\text{N-E-N}[\text{Si}(\text{CH}_3)_3]_2$   
(E = S, Se) AS PRECURSORS

After the early synthesis of the telluraheterocycles from  $\text{Se}(\text{NSO})_2$  or  $\text{Te}(\text{NSO})_2$ , other and sometimes more efficient synthetic routes were investigated. Trimethylsilyl-substituted compounds containing a S-N moiety were used successfully as synthons. The 8-membered ring  $\text{Cl}_2\text{Te}(\text{N}=\text{S}=\text{N})_2\text{TeCl}_2$  is prepared in almost quantitative yields from  $\text{TeCl}_4$  and  $(\text{CH}_3)_3\text{SiNSO}$  dissolved in  $\text{CH}_2\text{Cl}_2$  at  $60^\circ\text{C}$  (3 days) (see Scheme 24). As the starting materials are either commercially available or readily prepared, this procedure is superior to those already described (95CB11). The compound  $[(\text{CH}_3)_3\text{Si}]_2\text{N-S-N}[\text{Si}(\text{CH}_3)_3]_2$  is a very valuable reagent. With  $\text{TeCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at  $20^\circ\text{C}$  (2 days), it forms the already described  $\text{Cl}_2\text{TeTeNSN}$  in a 85% yield. It reacts with  $\text{TeF}_4$  at  $22^\circ\text{C}$  (2 days) in  $\text{CH}_2\text{Cl}_2$ , giving a 90% yield of the ionic compound,  $[\text{FTeTeNSN}^+][\text{TeF}_5^-]$  (see Scheme 25) (95CB11).

Replacement of one Te atom in a 5-membered ring by selenium or sulfur is achieved by using 1 : 1 mixtures of  $\text{TeX}_4$  and  $\text{SeCl}_4$  or  $\text{TeX}_4$  and  $\text{SCL}_2$ . These mixtures react with the  $[\text{C}(\text{CH}_3)_3\text{Si}]_2\text{N}_2\text{S}$  in  $\text{CH}_2\text{Cl}_2$  at  $22^\circ\text{C}$  (24 h)



SCHEME 24

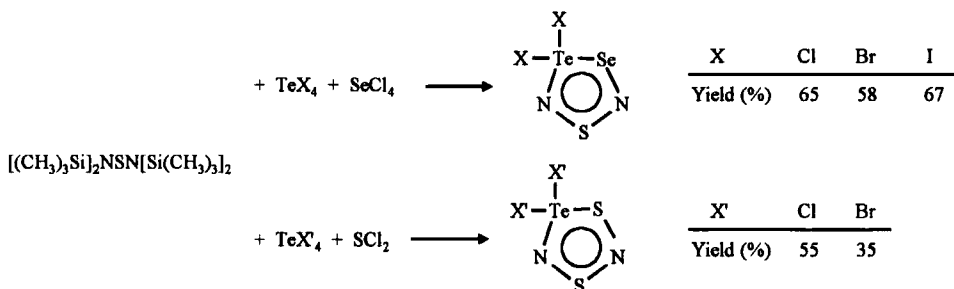


SCHEME 25

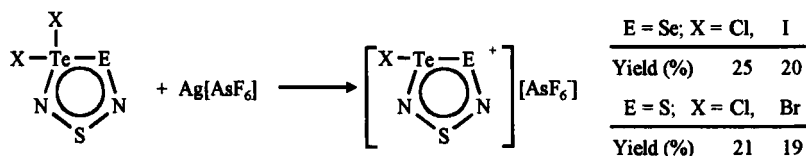
forming dihalogenothiaselenatelluradiazol or dihalogenodithiatelluradiazol (see Scheme 26). Metathetical reactions between the halogenated rings and  $\text{Ag}[\text{AsF}_6]$  in liquid  $\text{SO}_2$  yield the ionic compounds (see Scheme 27).

An unusual result is obtained when  $\text{Br}_2\text{TeSeNSN}$  is treated with  $\text{Ag}[\text{AsF}_6]$  under similar conditions. Stoichiometric amounts of  $[\text{BrSeSeNSN}^+][\text{AsF}_6^-]$  are formed rather than the expected  $[\text{BrTeSeNSN}^+][\text{AsF}_6^-]$ . In similar reactions compounds of the type  $[\text{XTeSNSN}^+][\text{Y}^-]$ , with  $\text{X} = \text{Cl}$  or  $\text{Br}$ ,  $\text{Y} = [\text{SbF}_6^-]$ ,  $[\text{BF}_4^-]$ , are obtained in low yield using  $\text{Ag}[\text{SbF}_6]$  or  $\text{Ag}[\text{BF}_4]$ . In the case of  $\text{X}_2\text{TeSNSN}$ , these metathetical reactions are solvent dependent. When  $\text{CH}_2\text{Cl}_2$  is used instead of  $\text{SO}_2$  as the solvent, dimeric dications are formed with two different counterions (see Scheme 28). These double salts are more soluble, and single crystals are readily obtained. The structure of  $[\text{ClTeSNSN}^+]_2[\text{Cl}^-][\text{AsF}_6^-]$  is determined by X-ray crystallography (94CB1865).

Interesting results are also obtained using  $[(\text{CH}_3)_3\text{Si}]_2\text{NSe}_x\text{N}[\text{Si}(\text{CH}_3)_3]_2$ ,  $x = 1, 2$  (95CB437). They react with  $\text{TeX}_4$  ( $\text{X} = \text{Cl}, \text{Br}$ ) in toluene at  $20^\circ\text{C}$  (24 h) to give 80 and 75% yields of the bicyclic compounds  $\text{X}_6\text{Te}_2\text{N}_2\text{Se}$ , containing an  $\text{N}=\text{Se}=\text{N}$  moiety (see Scheme 29). In the case of the diselenide



SCHEME 26



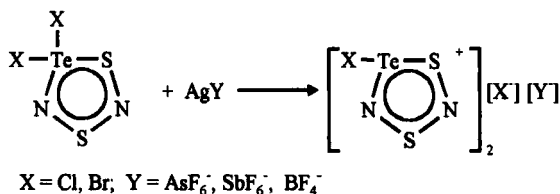
SCHEME 27

( $x = 2$ ), elemental selenium, which could not be separated from the heterocycle, is eliminated. They are thermally stable (decomposition without melting  $>200^\circ\text{C}$ ) and are characterized spectroscopically and by elemental analysis (95CB437).

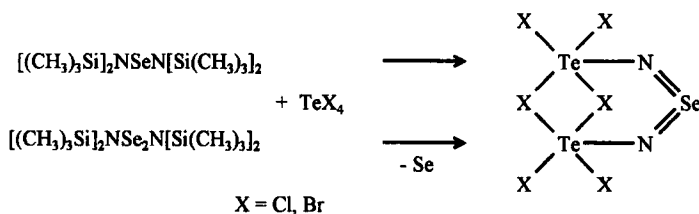
## F. DITELLURAETANES AND DITELLURADIAZETIDINES

The dimers of perfluorinated telluroketones are the first examples of 1,3-ditelluraetanes having  $sp^3$  hybridized carbon atoms. The only other known 4-membered ring with two tellurium atoms in the 1,3-position is the cyclic dimer of a telluroketone, which has  $sp^2$ -hybridized carbon atoms [81JCS(CC)829, 81TL1495, 81TL4199, 81ZOR667].

The unstable telluroketones  $\text{F}(\text{X})\text{C}=\text{Te}$  ( $\text{X} = \text{F}, \text{CF}_3$ ) dimerize at slightly above liquid nitrogen temperature, forming ditelluraetanes. Fluorine/halogen metathesis with boron trihalides gives the corresponding halogenated substances (see Scheme 30). Tetraiodo-1,3-ditelluraetane is made similarly by using  $(\text{CH}_3)_3\text{SiI}$  (93TH1, 93UP1). The tetrahalogenated ditelluraetanes are almost insoluble in common organic solvents except dimethylformamide, forming solvates of the formula  $\text{Cl}_2\text{CTe}_2\text{CCl}_2 \cdot 0.5 \text{ DMF}$ ,  $\text{Br}_2\text{CTe}_2\text{CBr}_2 \cdot \text{DMF}$  [93JSC(D)2547], and  $\text{I}_2\text{CTe}_2\text{CI}_2 \cdot \text{DMF}$  (93TH1, 93UP1). These are isolated and fully characterized. X-ray investigations with single crystals of  $\text{F}_2\text{CTe}_2\text{CF}_2$  and  $\text{CF}_3(\text{F})\text{CTe}_2\text{C}(\text{F})\text{CF}_3$  show that the  $\text{C}_2\text{Te}_2$  unit forms a planar rhombus with the following selected parameters:



SCHEME 28

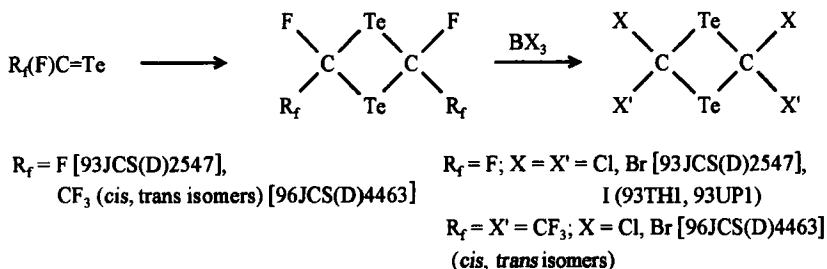


SCHEME 29

$\text{F}_2\text{CTe}_2\text{CF}_2$ :  $d(\text{Te}-\text{C}) = 2.191 \text{ \AA}$ ,  $d(\text{C}-\text{F}) = 1.359 \text{ \AA}$ ,  $d(\text{Te}-\text{Te}) = 3.236 \text{ \AA}$ .  
 $\angle(\text{CTeC}) = 78.9^\circ$ ,  $\angle(\text{TeCTe}) = 101.1^\circ$ ,  $\angle(\text{FCF}) = 105^\circ$  [93JSC(D)2547].  
*Trans*- $\text{CF}_3(\text{F})\text{CTe}_2\text{C}(\text{F})\text{CF}_3$  at 169 K:  $d(\text{Te}-\text{C}-1) = 2.21 \text{ \AA}$ ,  $d(\text{C}-1-\text{C}-2) = 1.47 \text{ \AA}$ ,  $d(\text{C}-1-\text{F}) = 1.44 \text{ \AA}$ ,  $d(\text{C}-2-\text{F}-3) = 1.40 \text{ \AA}$ ,  $\angle(\text{C}-1-\text{Te}-\text{C}-1) = 83.9^\circ$ ,  
 $\angle(\text{Te}-\text{C}-1-\text{Te}) = 96.1^\circ$  [96JCS(D)4463].

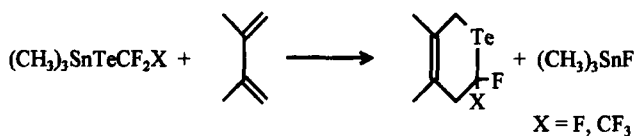
The highly reactive telluroketones and their cyclic dimers undergo  $[4 + 2]$ -cycloaddition reactions with 2,3-dimethylbutadiene, forming the corresponding 1-telluracyclohex-3-enes. If  $\text{F}_2\text{C}=\text{Te}$  is used, the yield is about 1%, but if the  $\text{F}_2\text{C}=\text{Te}$  is generated *in situ* from  $(\text{CH}_3)_3\text{SnTeCF}_3$ , it reacts with  $\text{CH}_2=\text{C}(\text{CH}_3)\text{C}(\text{CH}_3)=\text{CH}_2$  in  $\text{CHCl}_3$  at  $70^\circ\text{C}$ , giving a 50% yield of the product [93JSC(D)2547]. An equivalent reaction takes place using  $(\text{CH}_3)_3\text{SnTeCF}_2\text{CF}_3$  at  $150^\circ\text{C}$  (4 h), giving the  $\text{CF}_3$ -substituted derivative in an 86% yield [96JCS(D)4463] (see Scheme 31).

Attempts to synthesize molecules with a  $\text{Te}=\text{N}$  unity by treatment of  $\text{CF}_3\text{SN}[(\text{CH}_3)_3\text{Si}]_2$  with  $\text{TeCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at  $20^\circ\text{C}$  (24 h) failed. A yellow solid soluble in benzene, toluene, and tetrahydrofuran (THF) is obtained (see Scheme 32). The product is very sensitive to water. Recrystallization from THF yields single crystals solvated with two THF, and an X-ray analysis reveals a 4-membered  $\text{Te}_2\text{N}_2$  ring arrangement as shown in Scheme 32, with a distorted pseudo-octahedral tellurium atom of the form  $\text{OCl}_2\text{NN}^-\text{TeE}$  ( $\text{E}$  = free electron pair). The ligands Cl-1, Cl-2, O, and N oc-



SCHEME 30



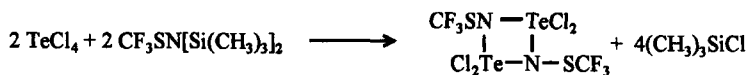


SCHEME 31

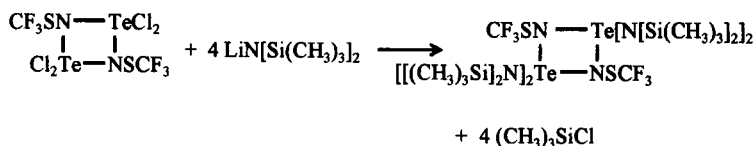
cupy equatorial and N' and E apical positions of the octahedron. The apical  $d(\text{Te}-\text{N}') = 2.017(3)$  is slightly shorter than equatorial  $d(\text{Te}-\text{N}) = 2.130(2)$  Å, probably due to a *trans* effect. A  $\pi$ -delocalization of the free electron pairs can be ruled out. The two different Te-Cl bond lengths  $d(\text{Te}-\text{Cl}-1) = 2.511(1)$  Å and  $d(\text{Te}-\text{Cl}-2) = 2.373(1)$  Å may also be explained by the *trans* effect. The distance  $d(\text{Te}-\text{O}) = 2.448(3)$  Å is characteristic of a coordinative Te-O interaction. The chlorine atoms can be totally replaced by an  $\text{N}[\text{Si}(\text{CH}_3)_3]_2$  group in the reaction with  $\text{LiN}[\text{Si}(\text{CH}_3)_3]_2$  at 50°C (24 h) in *n*-hexane, yielding 80% 1,1,3,3-tetrakis[bis-(trimethylsilyl)amido-2,4-bis(trifluoromethylthio)-1 $\lambda^4$ ,3 $\lambda^4$ ,2 $\lambda^3$ ,4 $\lambda^3$ -ditellur adiazetidene, (see Scheme 33) [95CB477]. This first  $[(\text{CH}_3)_3\text{Si}]_2\text{N}$ -substituted Te(IV) compound is a dark yellow viscous oil, soluble in benzene, hexane,  $\text{CH}_2\text{Cl}_2$ , and  $\text{CHCl}_3$ , that decomposes spontaneously in air with the elimination of tellurium. Diazetidines of the type  $(\text{F}_2\text{Te}-\text{NH})_2$  are synthesized by treating a suspension of  $\text{TeF}_4$  in ether with an ether solution of  $[(\text{CH}_3)_3\text{Si}]_2\text{NH}$  at 20°C (12 h), yielding 90% of a colorless compound that is stable up to >300°C and very hydrolytically sensitive. It is insoluble in normal organic and inorganic solvents. The high melting point (>300°C) and its insolubility indicate its polymeric nature. The corresponding chloroderivative cannot be made from  $\text{TeCl}_4$  and  $[(\text{CH}_3)_3\text{Si}]_2\text{NH}$ , but metathesis between  $(\text{F}_2\text{Te}-\text{NH})_2$  and  $(\text{CH}_3)_3\text{SiCl}$  in ether at 20°C (12 h) yields, almost quantitatively, a yellow, water-sensitive, insoluble, and high-melting substance that is probably polymeric (see Scheme 34). All diazetidienes do not explode on heating or by mechanical shock (96TH1,96UP1).

#### IV. Discussion of and Support for Possible Reaction Pathways

The three molecules  $\text{E}(\text{NSO})_2$  (E = S, Se, Te) have identical functional groups and are isostructural, differing only in the central atom E. However, their chemical reactivities are quite different. There are no significant



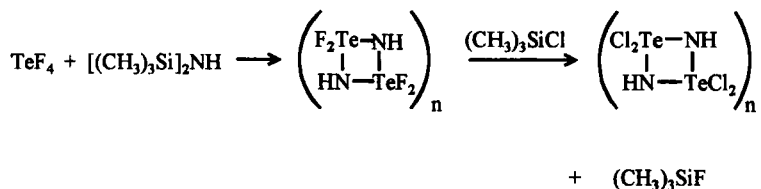
SCHEME 32



SCHEME 33

changes in structures and physical properties when sulfur is replaced by selenium or selenium by tellurium. Their chemical reactivities are substantially different due to the variable stability of intermediates. The two key reactions of  $\text{S}(\text{NSO})_2$  are those with  $\text{TiCl}_4$  and  $\text{SbCl}_5$  yielding polymeric  $(\text{S}_2\text{N}_2 \cdot \text{TiCl}_4)_x$  and the adduct  $\text{S}_4\text{N}_4 \cdot \text{SbCl}_5$ . In both reactions the first step can be postulated as an intramolecular condensation releasing  $\text{SO}_2$  and forming  $\text{S}_2\text{N}_2$ . The  $\text{S}_2\text{N}_2$  is either trapped by  $\text{TiCl}_4$  or dimerizes to  $\text{S}_4\text{N}_4$ , which reacts with  $\text{SbCl}_5$ , giving the 1 : 1 adduct  $\text{S}_4\text{N}_4 \cdot \text{SbCl}_5$ . The final products of the reactions of  $\text{S}(\text{NSO})_2$  generally correspond to the chemistry of  $\text{S}_4\text{N}_4$  but in some cases to that of  $\text{S}_2\text{N}_2$ , e.g., in the reaction of  $(\text{Ph}_3\text{P})_2\text{PtCH}_2=\text{CH}_2$  yielding  $(\text{Ph}_3\text{P})_2\text{PtS}_2\text{N}_2$ . It can be postulated that the decomposition of  $\text{S}(\text{NSO})_2$  observed in various reactions proceeds via  $\text{S}_2\text{N}_2$  to  $\text{S}_4\text{N}_4$  according to Scheme 35. Two planar  $\text{S}_2\text{N}_2$  rings are orientated in such a way that the sulfur atoms of one  $\text{S}_2\text{N}_2$  interact with the nitrogen atoms of the other, as described by Fukui *et al.* (78JPC1453) and as shown in Scheme 36, forming two new  $\sigma$ -(S-N) bonds S-1-N-3 and N-2-S-4, and weakening the  $\pi$ -bonds S-1-N-2 and S-4-N-3. A weak intermediate-range interaction of S-2 and S-3 must also be considered. The formation of  $\text{S}_4\text{N}_4$  with four coplanar N atoms takes place by deformation of the S-2-S-3 fulcrum, providing the most stable cage geometry by forming an additional weak S-1-S-4 bond.

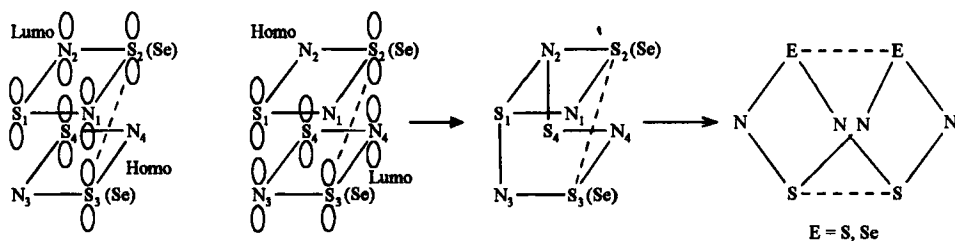
The chemistry of  $\text{Se}(\text{NSO})_2$  can be explained using the same first two steps. With  $\text{TiCl}_4$  it forms the analogous compound  $\text{SeNSN} \cdot \text{TiCl}_4)_n$  (see Scheme 13), and with Lewis and Brönsted acids such as  $\text{MF}_5$  ( $\text{M} = \text{As}, \text{Sb}, \text{Nb}$ ),  $\text{BF}_3$ , and  $\text{XSO}_2\text{OH}$  ( $\text{X} = \text{F}, \text{CF}_3$ ), the bis(1,3,4,2,5-thiadiselenadiazolium) dication with the corresponding counteranions is isolated (see Schemes 10, 37, and 38). The first step in these reactions is the quantitative



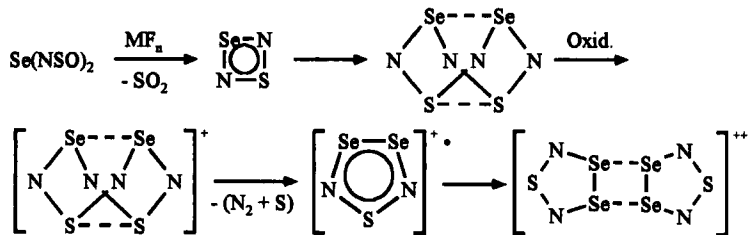
SCHEME 34



SCHEME 35

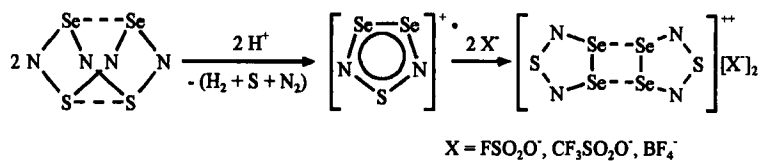


SCHEME 36



M = As, Sb, Nb; n = 5; B, n = 3

SCHEME 37



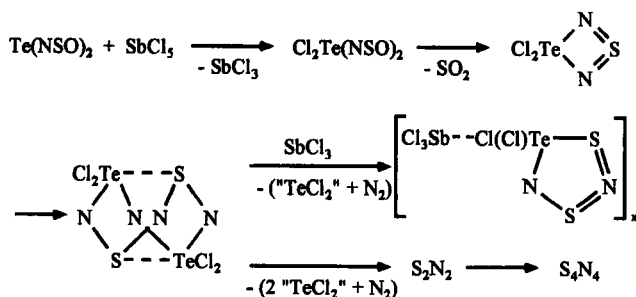
SCHEME 38

elimination of  $\text{SO}_2$ , which has been isolated and characterized by its IR spectrum, forming primary 1,3,2,4-thiaselenadiazete. This then dimerizes to an  $\text{S}_4\text{N}_4$ -type cage with two bridging sulfur atoms replaced by selenium atoms, analogous to the dimerization of  $\text{S}_2\text{N}_2$  described earlier (see Scheme 36), with the replacement of S-2 and S-3 by two Se atoms. However, the  $\text{S}_2\text{Se}_2\text{N}_4$  cage containing the  $\overline{\text{SeSeNSN}}$  ring frame is unstable and decomposes as shown in Schemes 37 and 38 to the final products. Among the intermediates postulated, two have been shown to exist, namely  $\overline{\text{SeNSN}}$  as an adduct with  $\text{TiCl}_4$  and the 5-membered radical cation by ESR-spectroscopy (88CJC1776; 91CB1895) showing a quintet with  $a_N = 3.006$  (91CB1895) and  $g = 2.01$  (90MI1). The decomposition of the cage  $\text{Se}_2\text{S}_2\text{N}_4$  to the radical cation  $[\overline{\text{SeSeNSN}}^+]$  is an oxidation. The Lewis acids  $\text{MF}_5$  ( $\text{M} = \text{As}, \text{Sb}, \text{Nb}$ ) act as oxidants, forming  $\text{MF}_3$ , which can be detected. The transformation of  $\text{Se}(\text{NSO})_2$  to the radical cation by the perfluorinated Brönsted acids  $\text{XSO}_2\text{OH}$  ( $\text{X} = \text{F}, \text{CF}_3$ ) via Scheme 38 is more complicated. Reduction of  $\text{H}^+$  to  $\text{H}_2$  according to Scheme 38 can be postulated. In the presence of  $\text{HF}$ , gaseous  $\text{H}_2$  would be formed together with two  $\text{F}^-$  ions, which then react with  $\text{BF}_3$  to form the counteranion  $[\text{BF}_4]^-$ . As no attempts were undertaken to confirm the liberation of  $\text{H}_2$ , this reaction step is therefore questionable. A different pathway must be discussed for the reactions of  $\text{Se}(\text{NSO})_2$  with chlorinating agents such as  $\text{SbCl}_5$ ,  $\text{PCl}_5$ ,  $\text{SeCl}_4$ , and  $\text{POCl}_3$ . In the first three cases an ionic 3-chloro-1,3,4,2,5-thiadiselenadiazolium moiety can be isolated, and with  $\text{POCl}_3$  a covalent  $\text{Cl}_2$   $\overline{\text{SeSeNSN}}$  ring is obtained. In any explanation of the formation of the exocyclic chlorinated 5-membered ring the chlorination process has to be considered. An initial chlorination step is not realistic, as all attempts to chlorinate  $\text{Se}(\text{NSO})_2$  to  $\text{Cl}_2\text{Se}(\text{NSO})_2$  have failed, but, as shown in Scheme 11, halogenation of the dication can be accomplished without difficulty and could therefore be the final step. The best description of this reaction pathway is the formation of the dication shown in Scheme 37 followed by chlorination to form the product isolated. No other known reactions appear to support this mechanism.

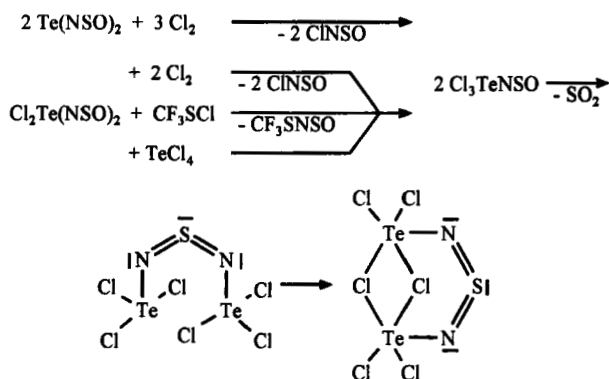
Transformation of  $\text{Te}(\text{NSO})_2$  into tellurium containing chalcogen-nitrogen heterocycles may provide some additional information about possible pathways. Treatment of  $\text{Te}(\text{NSO})_2$  with  $\text{SbCl}_5$  in  $\text{SO}_2$  gives a polymeric product of the formula  $[\text{SNSNTe}(\text{Cl})\text{Cl} \cdot \text{SbCl}_3]_x$ . Its structure has been established by X-ray crystallography, Fig. 4 (92MI1), and shows a 3-chlorodithiatelluradiazol ring. The formation of this 5-membered ring can be discussed in a manner similar to the analogous reaction of  $\text{Se}(\text{NSO})_2$ , and again the question arises at which stage chlorination occurs. As  $\text{Cl}_2\text{Te}(\text{NSO})_2$  can be synthesized by various methods (95CB477; 96TH1, 96UP1) it is clear that chlorination of  $\text{Te}(\text{NSO})_2$  must be considered in the first step. It has also been demonstrated that  $\text{Cl}_2\text{Te}(\text{NSO})_2$  undergoes in-

tramolecular condensation, yielding  $\text{Cl}_2 \overline{\text{TeNSN}}$  and  $\text{SO}_2$  (96TH1, 96UP1); see also p. 25 and Scheme 20. Thus, in the second step the  $\text{Cl}_2 \overline{\text{TeNSN}}$  ring should be able to dimerize to an unstable cagelike molecule, which then decomposes in two possible ways. Dimerization could take place according to Scheme 36 with tellurium atoms replacing S-3 and S-1. In this way a Te-S interaction, observed in the 5-membered ring (see Scheme 39) as a bond, can be rationalized.

In the presence of  $\text{SbCl}_3$  (formed from  $\text{SbCl}_5$ ) the cage decomposes to the chlorinated 5-membered ring, which reacts with  $\text{SbCl}_3$ , giving low yields of the polymer  $[\overline{\text{SNSNTe}(\text{Cl})\text{Cl}} \cdot \text{SbCl}_3]_x$ , " $\text{TeCl}_2$ " ( $\text{Te} + \text{TeCl}_4$ ), and  $\text{N}_2$ . The main reaction in the breakdown of the cage yields 2 moles of " $\text{TeCl}_2$ " plus  $\text{N}_2$  and  $\text{S}_2\text{N}_2$  that dimerize to the major product isolated,  $\text{S}_4\text{N}_4$ . These steps are illustrated in Scheme 39. The reaction pathway for the other tellurium containing key compound, the bicyclic  $\text{X}_6\text{Te}_2\text{N}_2\text{S}$ , has to involve the formation of an  $\text{X}_3\text{TeNSO}$  intermediate either by halogen/NSO metathesis or halogenation of  $\text{X}_2\text{Te}(\text{NSO})_2$ . Intermolecular condensation of 2 moles of  $\text{X}_3\text{TeNSO}$  gives  $\text{SO}_2$  and  $\text{X}_3\text{TeNSNTeX}_3$ . The latter rearranges to the final bicyclic product according to Scheme 40. The synthesis of tellurachalcogena-nitrogen heterocycles from  $\text{TeX}_4$  ( $\text{X} = \text{F}, \text{Cl}, \text{Br}$ ) and  $\text{Se}(\text{NSO})_2$  can be explained as follows: metathesis forming  $\text{X}_2\text{Te}(\text{NSO})_2$ ,  $\text{SO}_2$  elimination giving  $\text{X}_2\overline{\text{TeNSN}}$ , and cocyclization with  $\overline{\text{SeNSN}}$  [obtained by cyclization of  $\text{Se}(\text{NSO})_2$ ] yielding an 8-membered cage, Scheme 36, but replacing the Se atom in one ring with a  $\text{TeX}_2$  moiety. When  $\text{X} = \text{F}$  the cage is stabilized by cation formation with  $\text{TeF}_5^-$  as the counteranion. If  $\text{X} = \text{Cl}$  or  $\text{Br}$ , the cage decomposes to the 5-membered rings  $\text{X}_2\overline{\text{TeNSNSe}}$ , which have been isolated, plus nitrogen and sulfur. This is shown in Scheme 41 together with the formation of side products, which have been identified. The formation of the cage structured dication  $[\text{Te}_2\text{S}_2\text{N}_4]^{++}$  from 2 moles of  $\text{Cl}_2\overline{\text{TeTeNSN}}$  and 6 moles of  $\text{AsF}_5$  is best explained by assuming that  $\text{AsF}_5$  acts initially as a fluorinating agent yielding  $\text{F}_2\overline{\text{Te}(\text{Cl}_2)\text{Te}(\text{F}_2)\text{N}=\text{S}=\text{N}}$ , which subsequently

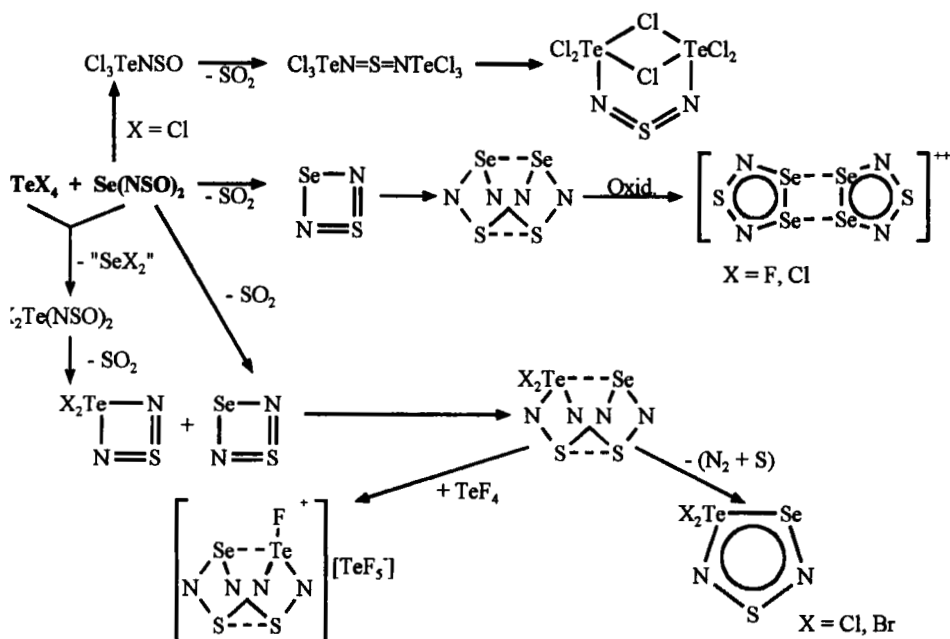


SCHEME 39

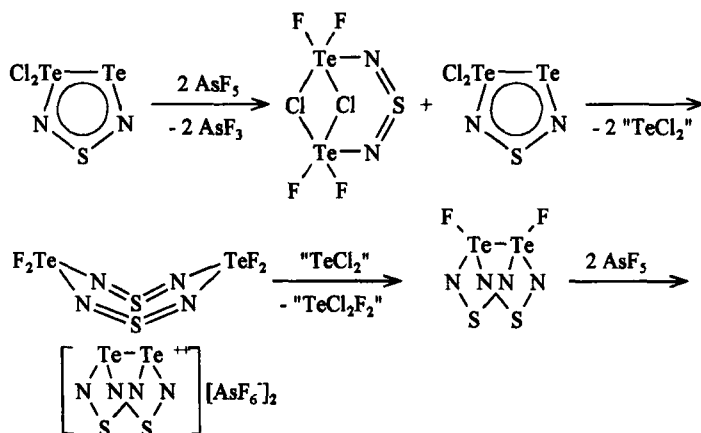


SCHEME 40

reacts with another mole of  $\text{Cl}_2$   $\overline{\text{TeTeNSN}}$  giving  $\text{F}_2\text{Te}(\text{N}=\text{S}=\text{N})_2\text{TeF}_2$  and two moles of "TeCl<sub>2</sub>." The latter might partially defluorinate the former, forming a Te-Te bond. With two moles of  $\text{AsF}_5$  the product is obtained as shown in Scheme 42. No convincing explanation can be postulated for the formation of the nitrogen-bridged cage  $[\text{SeS}_3\text{N}_5^+][\text{AsF}_6^-]$  (see Scheme 13).



SCHEME 41



SCHEME 42

## V. Summary and Future Developments

The three synthons  $\text{E}(\text{NSO})_2$  ( $\text{E} = \text{S}, \text{Se}, \text{Te}$ ), although isostructural, differ significantly in their chemical behavior, due mainly to the varying stability of the intermediates formed in their reactions. Specifically, the compounds  $\text{Se}(\text{NSO})_2$  and  $\text{Te}(\text{NSO})_2$  have enabled new procedures for the synthesis of selenium and tellurium heterocycles to be developed. For compounds such as  $\text{X}_2\text{Te}(\text{NSO})_2$  ( $\text{X} = \text{F}, \text{Cl}$ ), it would be interesting to know if these compounds are also able to eliminate  $\text{SO}_2$  and if so, how, inter- or intramolecularly. As the reaction pathways are not fully understood, more significant experimental work is needed.

The type of chemistry outlined here should also be extended to other elements, e.g.,  $\text{B}$ ,  $\text{Si}$ ,  $\text{Ge}$ ,  $\text{Sn}$ , etc., by attempting to prepare compounds like  $\text{R}_{3-n}\text{B}(\text{NSO})_n$ ,  $\text{R}_{4-n}\text{E}(\text{NSO})_n$ ,  $\text{E} = \text{Si}, \text{Ge}, \text{Sn}$ , and  $\text{R}_2\text{Te}(\text{NSO})_2$  with  $\text{R}$  = halogen, organo, or perfluoro-organo substituents.

The preparation of the very reactive perfluorinated tellurocarbonyls such as  $\text{F}_2\text{C}=\text{Te}$  and  $\text{CF}_3(\text{F})\text{C}=\text{Te}$  opened another totally new way into tellurium heterocyclic chemistry. These tellurocarbonyls dimerize at room temperature to stable perfluorinated 1,3-ditelluretanes, which at elevated temperatures undergo  $[4 + 2]$ -cycloadditions with 1,3-dimethylbutadiene, forming fluorinated 1-telluracyclohex-3-enes. This type of reaction can be extended to other "ene" synthons. Meanwhile similar reactions have been reported for 2,2,4,4-tetrakis(trifluoromethyl)-1,3-ditelluraetane, which was synthesized by the pyrolysis of  $(\text{CH}_3)_3\text{SnTeCF}(\text{CF}_3)_2$  (96UP2).

Finally, it was a great surprise to discover that tellurium, a typical semi-metal, undergoes reactions typical of covalent compounds and that none of the  $\text{Te}-\text{N}$  bonds containing heterocyclic molecules so far prepared tend to explode.

## ACKNOWLEDGMENTS

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72AG(E)642  
72IC1151  
75CB2340  
76JINC(S)213  
78JCS(CC)212  
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# Chemistry of Pyrido[2,1-*c*][1,4]oxazines, Pyrido[2,1-*c*][1,4]thiazines, Pyrido[1,2-*a*]pyrazines and Their Benzologues

ISTVÁN HERMECZ

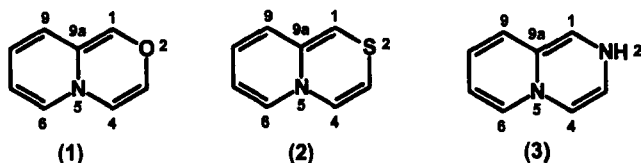
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I. Introduction .....	145
II. Structure .....	148
A. Pyrido[2,1- <i>c</i> ][1,4]oxazines and Their Benzo Derivatives .....	148
B. Pyrido[2,1- <i>c</i> ][1,4]thiazines and Their Benzo Derivatives .....	155
C. Pyrido[1,2- <i>a</i> ]pyrazines and Their Benzo Derivatives .....	157
III. Reactivity .....	163
A. Pyrido[2,1- <i>b</i> ][1,4]oxazines and Their Benzo Derivatives .....	163
B. Pyrido[1,2- <i>a</i> ][1,4]thiazines and Their Benzo Derivatives .....	181
C. Pyrido[1,2- <i>a</i> ]pyrazines and Their Benzo Derivatives .....	187
IV. Synthesis .....	210
A. Pyrido[2,1- <i>c</i> ][1,4]oxazines and Their Benzo Derivatives .....	210
B. Pyrido[2,1- <i>c</i> ][1,4]thiazines and Their Benzo Derivatives .....	226
C. Pyrido[1,2- <i>a</i> ]pyrazines and Their Benzo Derivatives .....	233
V. Applications and Important Compounds .....	252
A. Pyrido[2,1- <i>c</i> ][1,4]oxazines and Their Benzo Derivatives .....	252
B. Pyrido[2,1- <i>c</i> ][1,4]thiazines and Their Benzo Derivatives .....	253
C. Pyrido[1,2- <i>a</i> ]pyrazines and Their Benzo Derivatives .....	253
References .....	255

## I. Introduction

The chemistry of the pyrido[2,1-*c*][1,4]oxazines (**1**), pyrido[2,1-*c*][1,4]thiazines (**2**), and pyrido[2,1-*a*]pyrazines (**3**) (Scheme 1) and their benzologues (**4**)–(**18**) (Schemes 2–4) has not been systematically reviewed. Only Mosby's book in 1961 treated the early articles on pyrido[2,1-*c*][1,4]thiazines (61CH1182), pyrido[2,1-*a*]pyrazines (61CH1188), 5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines (61CH1180), pyrazino[1,2-*a*]quinolines (61CH1192), pyrido[1,2-*a*]quinoxalines (61CH1191), and pyrido[1,2,3-*de*]quinoxalines (61CH1193).

In the present review the primary chemical literature up to the middle of 1997 has been surveyed. *Chemical Abstract* Subject and Chemical Sub-

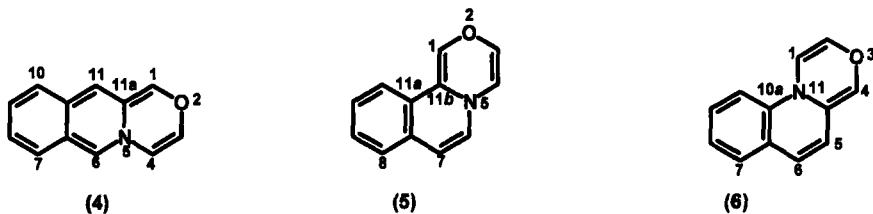
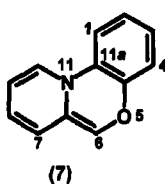


SCHEME 1

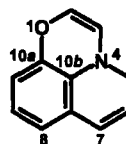
stance Indexes up to and including Volume 125 have been searched. Throughout this chapter the names and numbering style favored by *Chemical Abstracts* are used and indicated on Schemes 1–4.

Optically active pipecolic acid and its derivatives can be prepared via 4-phenylpyrido[2,1-*c*][1,4]oxazin-1-one derivatives. Representatives of the third generation of quinoline-3-carboxylic acid antibacterial agents ofloxacin (**19**), its levorotatory enantiomer, levofloxacin (**20**), and rifloxacin (**21**) have gained wide acceptance for the treatment of bacterial infections of the respiratory and urinary tracts, skin, and soft tissues, as well as sexually transmitted diseases, and pazufloxacin (**22**) is under development. Other 10-aryl-9-fluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids and 7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids exhibit mammalian topoisomerase II inhibitory activity.

#### Benzo Derivatives of Pyrido[2,1-*c*][1,4]oxazine

[1,4]Oxazino[4,3-*b*]isoquinoline[1,4]Oxazino[3,4-*a*]isoquinoline[1,4]Oxazino[4,3-*a*]quinoline

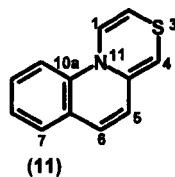
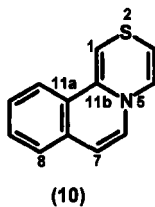
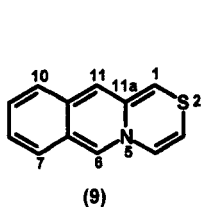
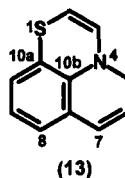
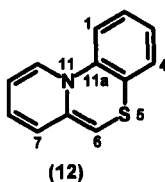
(7)



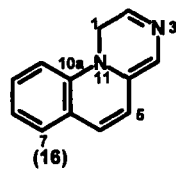
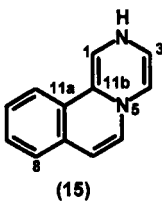
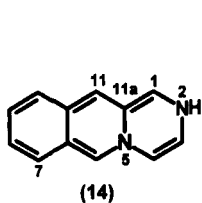
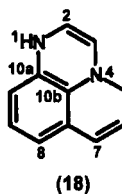
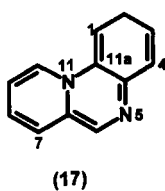
(8)

Pyrido[2,1-*c*][1,4]benzoxazine5*H*-Pyrido[1,2,3-*de*]-1,4-benzoxazine

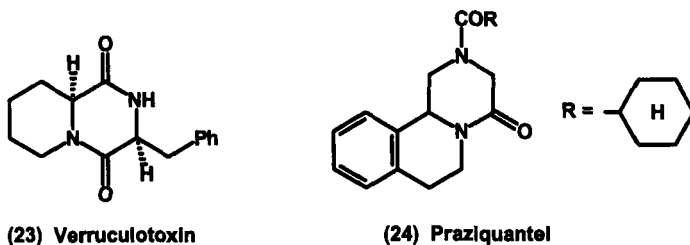
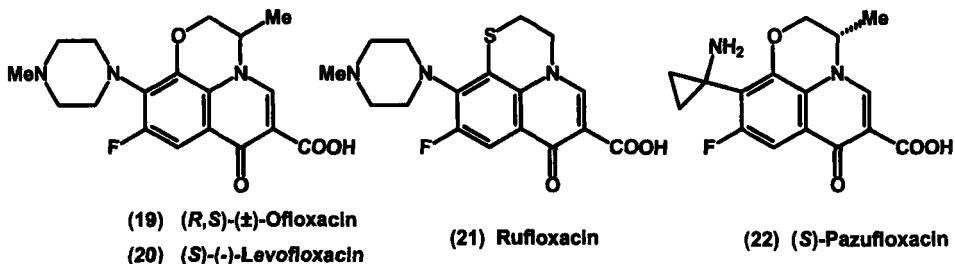
SCHEME 2

Benzo Derivatives of Pyrido[2,1-*c*][1,4]thiazine[1,4]Thiazino[4,3-*b*]isoquinoline[1,4]Thiazino[3,4-*a*]isoquinoline[1,4]Thiazino[4,3-*a*]quinolinePyrido[2,1-*c*][1,4]benzothiazine5*H*-Pyrido[1,2,3-*de*]-1,4-benzothiazine

SCHEME 3

Benzo Derivatives of Pyrido[1,2-*a*]pyrazine2*H*-Pyrazino[1,2-*b*]isoquinoline2*H*-Pyrazino[2,1-*a*]isoquinoline1*H*-Pyrazino[1,2-*a*]quinoline2*H*-Pyrido[1,2-*a*]quinoxaline1*H*,5*H*-Pyrido[1,2,3-*de*]quinoxaline

SCHEME 4



Verruculotoxin (**23**) is produced by the fungus *Penicillium verrucosum* Peyronel. Praziquantel (**24**) is widely applied for the treatment of schistosomes- and cestode-caused infections in both veterinary and human therapies. Other compounds of these ring systems have aroused much interest owing to their valuable pharmacological properties.

In the following sections the physicochemical and spectroscopic properties, reactions, syntheses, and, more briefly, utilization of these ring systems are discussed. Within the individual sections the pyrido[2,1-*c*][1,4]oxazines and their benzologues, pyrido[2,1-*c*][1,4]thiazines and their benzologues, and pyrido[2,1-*a*]pyridazines and their benzologues are dealt with.

## II. Structure

### A. PYRIDO[2,1-*c*][1,4]OXAZINES AND THEIR BENZO DERIVATIVES

#### 1. Thermodynamic Aspects

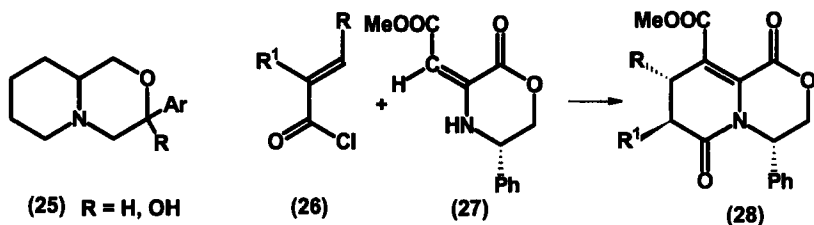
Ofloxacin (**19**) contains two proton-binding sites of similar basicity: position 4 of the piperazine moiety and the 6-carboxyl group (91MI7). The protonation macroconstants and microconstants have both been determined (92JPS592, 92MI16; 93MI6; 94MI8, 94MI19; 95MI22). The protonation constant of ofloxacin was determined in LiCl solutions of various concentrations at 293, 303, and 313 K (92TAL665). The stability constants of metal complexes of ofloxacin (**19**) were determined by means of po-

tentiometry and spectrophotometry (92CPB692). The ofloxacin-Cu(II) complexes were investigated by spectrophotometry and polarography (96TAL2123). The complex formations of 10-substituted 9-fluoro-3(*S*)-methyl-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids with various metal cations were investigated by pH titrations, NMR, and spectrophotometry (96CPB1425). Ofloxacin was determined by potentiometry and conductometry (92PHA642), by spectrophotometry (94MI13, 94MI17), by complexometric titration (94MI17), by an adsorptive stripping voltametric method (90MI3), by a TLC assay (89MI1), and by titrimetric methods (91MI6). Physicochemical properties of levofloxacin (91MI15) and pazufloxacin (95MI14) were clarified by solubilities,  $pK_a$  and hygroscopicity (91MI15). The solubility and hygroscopicity of **19** were investigated (89MI15; 91MI7). The effects of pH, temperature, and NaCl concentration on aqueous solubility of ofloxacin were investigated (90MI9). The solubility and apparent partition coefficient of other 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids were also determined (94CPB1442; 95MI14). The polarographic and voltametric behavior of ofloxacin (**19**) was investigated (95ACA49).

The 1-octanol–water partition coefficients of **19** and **20** have been reported by different groups (85MI3; 91MI15; 92AF70, 92MI13, 92MI20). Lipophilicity of **19** was determined by a micromethod, too (88MI8). The pH partition profile of **19** between pH 4 and 10 pointed to maximum partitioning at the isoelectric point (92MI13). Partition coefficients of ester prodrugs of **19** were also determined in water–*n*-octanol (92AF70). The lipophilicity of **19** was characterized by TLC investigations (94MI3). Supercritical fluid chromatography was applied to the investigation of **19** (91MI5). The chiral separation of **19** and the *N*-ethyl homolog of levofloxacin was studied by capillary affinity zone electrophoresis in the presence of bovine serum albumin (94MI6; 95MI8). Pazufloxacin was determined by nonaqueous titration and by HPLC (95MI14).

Different HPLC methods have been developed for the determination of antibacterial **19** and its enantiomers in biological fluids and formulations [85MI4; 86MI2, 86MI5, 86MI6, 86MI11, 86MI12; 87MI7; 88MI2–88MI6, 88MI6, 88MI9, 88MI14; 89MI2, 89MI8–89MI10; 91MI4, 91MI8, 91MI11, 91MI19, 91MI20; 92MI2, 92MI18, 92MI21; 93MI11, 93MI16, 93MI19, 93MI20, 93MI23; 94ACA215, 94FES407, 94MI1, 94MI2, 94MI7, 94MI9, 94MI12, 94MI16, 94MI18, 94MI21, 94MI23; 95KFZ(5)62, 95MI4, 95MI6, 95MI19, 95MI21; 96MI2, 96MI3]. The influence of pH on the HPLC retention of **19** has been investigated (91MI4; 93MI6; 94MI4, 94MI5). HPLC methods have similarly been developed (90MI7), and applied for the determination of (+)- and (–)-ofloxacin in biological fluids (88MI1, 88MI7). The optical purity of **20** was determined by HPLC (89MI12). A sensitive

and selective method involving isochratic HPLC has been developed for the simultaneous determination of **20** and its metabolites in biological fluids (91MI2). Other 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids were also determined by HPLC (95MI1).



Ionization constants, partition coefficients in water-*n*-octanol, and TLC  $R_M$  values of **25** (R = OH, Oalkyl) were determined [90AP(323)53].

## 2. Theoretical Calculations

The net charges on some representative atoms of different antibacterial 10-dimethylamino-9-fluoro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids, the energy levels of the HOMO and LUMO electrons, and the dipole moments were calculated by using molecular mechanics based on the MAXIMIN II and AM1 programs with geometry optimization (91JHC1067). A structure-activity relationship study was made by the computer automated structure evaluation program to study a series of quinolone antibacterials, including ofloxacin, on DNA gyrase inhibition as well as MICs against several strains of Gram-positive and Gram-negative bacteria (87AAC1831). Structure-activity relationship of quinolone antibacterials, including ofloxacin, was studied by MMP1 and CNDO/2 methods (94MI20), by electrotopological state index for atoms (94MI15). A receptor model was suggested for antibacterial quinolone, including ofloxacin, on the basis of the energy profile calculation by MO methods (91JMC131). The torsional angles and the spatial domain around the ring N-substituent of quinoline-3-carboxylic acids, among them *N*-desmethyl ofloxacin, were investigated by molecular modeling studies (93MI10).

AM1 calculations suggested that in the formation of methyl 4-phenyl-1,6-dioxo-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylates (**28**) from acryloyl chloride derivatives **26** and 1,4-oxazine **27** is favored over the hetero-Diels-Alder condensation (96JOC5736).

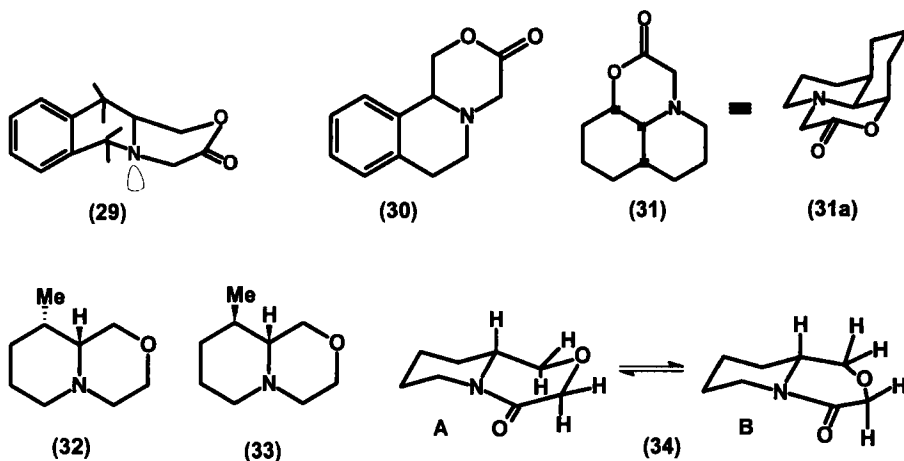
## 3. UV and Fluorescence Spectroscopy

Spectrophotometric methods were developed for the determination of **19**, using *o*-hydroxyhydroquinonephthalein-iron(III) complex (87CPB865),

or eosin and Pd(II) ion (87CPB5004). Ofloxacin was determined in biological fluid by fluorescence spectroscopy [90MI1; 93JAP(K)93/203578]. Spectrophotometry (92MI17, 92MI19) and spectrofluorometry (91MI20; 92MI14, 92MI17) were applied in the determination of **19**.

#### 4. IR Spectroscopy

The strong Bohlmann bands in the IR spectra indicate the *trans*-fused conformations of the 9-methyl epimers of **25** (R = OH) and other perhydropyrido[2,1-*c*][1,4]oxazines [72JCS(P2)1374, 72OMR(4)283; 76JMC 334; 78JMC460; 92CPB652], perhydropyrido[2,1-*c*][1,4]oxazin-3-ones [72OMR(4)509], and the heterocycles of 1,6,11,11a-tetrahydro[1,4]oxazino[4,3-*b*]isoquinolin-3(4*H*)-one (**29**), 1,6,7,11*b*-tetrahydro[1,4-]oxazino[3,4-*a*]isoquinolin-3(4*H*)-one (**30**) and *cis*-7*a*,11*a*,11*b*-H-perhydropyrido[1,2,3-*de*]-1,4-benzoxazin-2-one (**31**) [72OMR(4)509]. Replacement of the protons of the 4-methylene group by deuterium results in replacement of the 2810 and 2760 cm<sup>-1</sup> bands in the IR spectra of **32** and **33** by a band at 2785–2790 cm<sup>-1</sup> [72JCS(P2)1374].



#### 5. <sup>1</sup>H NMR Spectroscopy

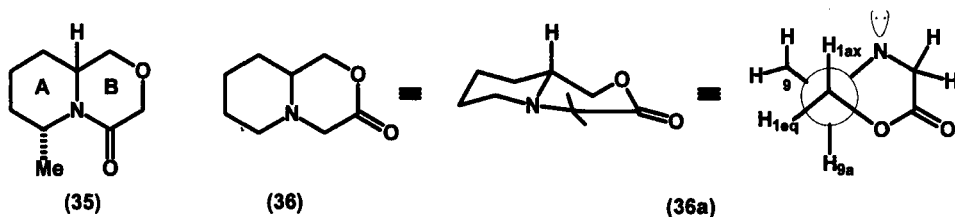
*a. Fully Saturated Ring Systems.* Conformational analysis of the epimers of 9-methylperhydropyrido[2,1-*c*][1,4]oxazines (**32**) and (**33**) and the desmethyl derivative confirmed the presence of the two-chair *trans*-fused conformation [72JCS(P2)1374].

<sup>1</sup>H NMR investigations [conformational analysis, NOE experiments, and utilization of the lanthanide shift reagent Eu(fod)<sub>3</sub>] indicated the presence of a *trans*-fused bicyclic system with an equatorial 3-aryl group in com-



pounds **25** ( $R = H$ ) (78JMC460), and an equatorial substituent in other 3-substituted perhydropyrido[2,1-*c*][1,4]oxazines (92CPB652). Epimerization of **25** ( $R = OH$ ) at C-3 via a ring-chain tautomerism was not observed in  $CDCl_3$  or pyridine- $d_5$  at 25–100°C (78JMC460).

Careful analysis of the coupling constants of perhydropyrido[2,1-*c*][1,4]oxazin-4-one (**34**) and its monosubstituted derivatives indicated that the 1,4-oxazinone moiety adopts energetically favorable conformation A or a structure close to this in which the ring O atom and the angular H are on the same side of the plane defined by C-3–C-4–O–N-5 [72OMR(4)283]. The geminal coupling constant of the 3-methylene protons is around 16 Hz, due to a hyperconjugative contribution from the lactam carbonyl group. The equatorial H of the 6-methylene group is deshielded because this proton lies in the plane of the lactone carbonyl group ( $\delta_{Heq} \approx 4.30$ –4.70 ppm). The geminal coupling constant of the 6-methylene protons is usually in the range –13 to –14 Hz. The 1-, 7-, and 9-monosubstituted epimers of perhydropyrido[2,1-*c*][1,4]oxazin-4-one (**34**) adopt conformations similar to that of the unsubstituted **34**, containing the substituent in the equatorial or axial position. Conformational analysis of the *cis*-6,9a-H-6-methyl derivative **35**, containing an equatorial methyl group, revealed that it contains a similar ring B conformation as the aforementioned derivatives, but piperidino ring A undergoes distortion to decrease the serious 1,3-allyl strain between the methyl group and the lactam carbonyl group [72OMR(4)283].



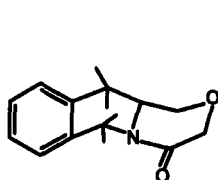
Conformational analysis of perhydropyrido[2,1-*c*][1,4]oxazin-3-ones suggested that **36** and its *cis*-1,9a-H-1-methyl, -ethyl, *cis*-6,9a-H-6-methyl, *cis*-8,9a-H-8-methyl and epimers of 7- and 9-methyl and 1-phenyl derivatives exist in a *trans*-fused conformation **36a** with a chair piperidine ring and a half-chair perhydrooxazinone ring in which both  $H_{1ax}$  and  $H_{9a}$  are axial, rather than in the classical half-chair in which the C-1 methylene bonds are pseudoaxial and pseudoequatorial ( $J_{vic} \sim 10.8$  and  $-3.5$  Hz) [72OMR(4)509]. The nodal plane of the 3-carbonyl group bisects the C-4 methylene group, and the nitrogen lone pair and the  $4_{ax}$ -H are parallel in conformation **36**, and therefore  $J_{gem}$  for the 4-methylene protons lies between –17.4 and –17.8 Hz. The similar values of the coupling constant  $J_{gem}$  (–17.5 Hz) for the C-3 methylene protons and chemical shifts of these protons ( $\delta \sim 3.40$  and 2.56 ppm) in *cis*-7a,10a,10b-H-perhydropyrido[1,2,3-

*de*][1,4]benzoxazin-2-one (**31**) as well as for the C-4 methylene protons of **36** ( $J_{\text{gem}} \sim -17.5$  Hz, and  $\delta \sim 3.34$  and 2.63 ppm in benzene) point to the presence of the *trans*-fused conformation of the heterorings of **31a** [72OMR(4)509]. The geminal coupling constant of  $-11.3$  Hz for 6-methylene of *cis*-7,9*a*-H-7-methyl derivative of **36** was found in  $\text{CCl}_4$  [71OMR(3)263].

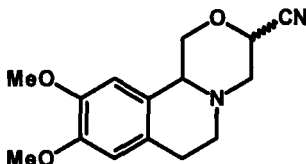
The benzene-induced solvent shifts (relative to  $\text{CCl}_4$  solution) of perhydropyrido[2,1-*c*][1,4]oxazin-3-one (**36**) and -4-one (**34**) and their monosubstituted derivatives have been studied [72OMR(4)283, 72OMR(4)509]. The structure of a *trans*-3,9*a*-H-3-[(aroylamino)methyl]perhydropyrido[2,1-*c*][1,4]oxazine was confirmed on the basis of coupling constants and NOE measurements in  $^1\text{H}$  NMR experiments (92CPB652).

b. *Partly Saturated Ring Systems.* The piperidine ring adopts a half-chair conformation in both 1,6,11,11*a*-tetrahydro[1,4]oxazino[4,3-*b*]isoquinolin-4(3*H*)-one (**37**) [72OMR(4)283] and -3(4*H*)-one (**29**) [72OMR(4)509], and the values ( $-17.2$  Hz and  $-15.4$  Hz, respectively) of the geminal coupling constant between the C-6 methylene protons indicate that the plane of the aromatic ring bisects the C-6 methylene group. The conformation of the oxazine ring in **29** resembles a classical half-chair with one pseudoaxial and one pseudoequatorial C-1 methylene proton ( $J_{1\text{ax},11\text{a}} \sim 8.9$  Hz,  $J_{1\text{eq},11\text{a}} \sim 3.4$  Hz), but the geminal coupling constant ( $J_{\text{gem}} \sim -17.9$  Hz) between the C-4 protons indicates a slightly different orientation of the carbonyl group with respect to the C-4 methylene [72OMR(4)509].

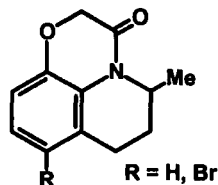
Conformational analysis of 1,6,7,11*b*-tetrahydro[1,4]oxazino[3,4-*a*]isquinolin-3(4*H*)-one (**30**) suggests a similar conformation for the oxazinone ring as that present in **36**, although the piperidine moiety of **30** is a half-chair [72OMR(4)509]. The coupling constants confirm the presence of *trans*-fused heterorings in the C-3 epimers of 1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline (**38**), with a chair oxazine ring and a half-chair piperidine ring (78JMC785).



(37)



(38)



(39)

The methyl group occupies an axial position in the half-chair conformation of the tetrahydropyridine moiety in pyrido[1,2,3-*de*]-1,4-benzoxazin-3-ones (**39**) in order to avoid the serious 1,3-allylic strain between the

equatorial methyl group and the carbonyl group in the alternative conformation (73T2571). 6-Bromo-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione contains an axial Br atom stabilized by an anomeric effect (72AJC1283).  $^1\text{H}$  NMR spectra of ofloxacin were measured in acidic, basic, and DMSO- $d_6$  solutions (94MRC192). An accurate  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR study on **19** was reported (96MI12).

## 6. $^{13}\text{C}$ NMR Spectroscopy

The *Z* and *E* geometric isomers of 3-alkoxycarbonylmethylene-3,4,5,6-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-2-one differ in the coupling constant of C-3 with the vinyl proton (5.6 Hz and 11.3 Hz, respectively) (78HCA607).  $^{13}\text{C}$  NMR spectra of ofloxacin (**19**) were measured in acidic, basic, and DMSO- $d_6$  solutions (94MRC192).

## 7. $^{19}\text{F}$ and $^{15}\text{N}$ NMR Spectroscopy

An accurate  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR study on **19** was reported (96MI12).  $^{19}\text{F}$  and  $^1\text{H}$  NMR spectroscopy were used to investigate **19** in the presence of EDTA in urine (92MI25). C-F coupling constants were determined in the case of **19** (94MRC192). Ofloxacin was quantitatively determined in some pharmaceuticals by  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectroscopy (95MI11).

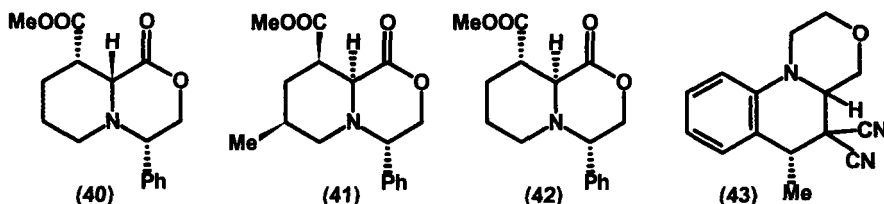
## 8. Mass Spectrometry

Unique fragmentation behavior of **19** and its desfluoro derivative was observed during molecular mass determination by methane negative chemical ionization mass spectrometry (91OMS669). Formation of a radical anion, which underwent a retro-Diels-Alder reaction in the gas phase to give a fragment ion by the loss of neutral propene was noted. Ofloxacin was characterized by electrospray mass spectrometry (95RCM1038), and an electron impact/Fourier transform ion cyclotron resonance mass spectrometry method (95MI13). Metabolites of **19** were identified by mass spectrometry (86MI7).

## 9. X-Ray Investigations

X-ray study of **39** (R = Br) showed the presence of an axial methyl group in a half-chair tetrahydropyridine ring (73T2571). The structure of the perchlorate salt of **19** was determined by means of X-ray investigations (91MI12). The solid-state structures of (4*S*)-derivatives of 4-phenyl-1-oxoperhydropyrido[2,1-*c*][1,4]oxazine-9-carboxylates **40–42** (95TL1657;

96JOC5736), and 1,2,4,4*a*,5,6-hexahydro[1,4]oxazino[4,3-*a*]quinoline **43** (89JOC209) were also determined by X-ray investigations.



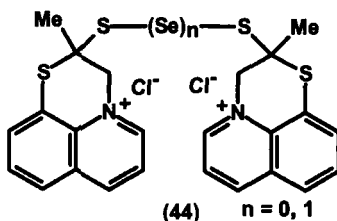
## B. PYRIDO[2,1-*c*][1,4]THIAZINES AND THEIR BENZO DERIVATIVES

### 1. Thermodynamic Aspects

The dissociation constant and solubilities of rifloxacin HCl (**21** HCl) were measured (89MI4). An adsorptive stripping voltametric method with a hanging Hg drop electrode was developed for the determination of **21** in tablets and biological fluids (95MI20).

### 2. Theoretical Calculations

A molecular orbital study has been carried out on diethyl 10-oxo-6,10-dihydro-6*H*-pyrido[2,1-*c*][1,4]benzothiazine-7,9-dicarboxylate. Full geometry optimization was performed using the AMPAC suite of programs (QEPE 506) in the AM1 parametrization (93MI1). The net charges on some representative atoms in different 10-dimethylamino-9-fluoro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids, the energy levels of the HOMO and LUMO electrons, and the dipole moments have been calculated (91JHC1067). The torsional angles and the spatial domain around the ring N-substituent of quinoline-3-carboxylic acids, among them 2-methyl-*N*-desmethyl rifloxacin were investigated by molecular modeling studies (93MI10). A quantum chemical study of the molecular and electronic structure of 2,2'-dithiobis(2-methyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium) species (**44**, *n* = 0) employed semiempirical MNDO and AM1 methods (95IZV2359).



### 3. Chromatographic Investigations

The  $R_M$  values of **21** and its 3-fluoromethyl derivative were measured at pH 1.2 and 9.0 by a reversed-phase TLC system (94MI3). Different HPLC assays have been developed to investigate the purity and the fate of rifloxacin (**21**) in biological fluids (90MI11; 91MI3, 91MI16; 92MI1, 92MI3, 92MI9). The influence of pH and organic modifiers on the HPLC retention of **21** has been investigated (94FES407). Levels of theophylline and **21** (95MI24), furprofen and **21** (96MI10), fenbufen, felbinac, and **21** (96MI1) were simultaneously determined by HPLC methods in human plasma. The capacity factor of 10-(*trans*-2-methyl-3-amino-1-azetidiny)-9-fluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid was determined in a reversed-phase HPLC system (94JMC4195).

### 4. UV and Fluorescence Spectroscopy

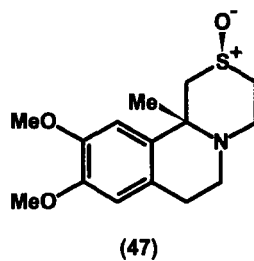
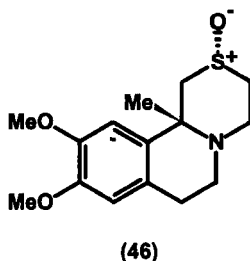
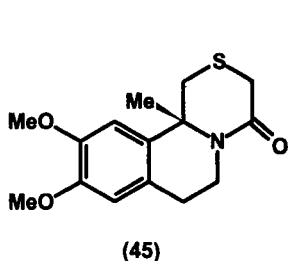
Fourth-derivative UV spectrophotometry was applied for the simultaneous determination of levels of **21** and its sulfoxide impurity (91FES979), and second-derivative UV spectrophotometry for that of **21** and furprofen (94FES527). A fluorometric method was developed for determination of the level of **21** in biological fluids (89MI16).

### 5. IR Spectroscopy

The *trans*-fused conformation of the heterorings of 9,10-dimethoxy-11*b*-methyl-1,3,4,6,7,11*b*-hexahydro[1,4]thiazino[3,4-*a*]isoquinoline was indicated by the appearance of Bohlmann bands in its IR spectrum (80JHC449).

### 6. $^1\text{H}$ NMR Spectroscopy

$1\text{-H}_{\text{ax}}$  in perhydropyrido[2,1-*c*][1,4]thiazin-4-ones in benzene- $\text{d}_6$  or in benzonitrile absorbs at higher field than does  $1\text{-H}_{\text{eq}}$ , which is the reversal of the normal situation for protons adjacent to sulfur, in as much as equatorial protons have been found to absorb at higher field than axial protons, this being attributed to the diamagnetic anisotropy of the C-S bond [72OMR (4)283].  $6\text{-H}_{\text{eq}}$  in 1,3,4,6,7,11*b*-hexahydro[1,4]thiazino[3,4-*a*]isoquinolin-4-one **45** is deshielded by the anisotropy of the neighboring lactam carbonyl, and a *trans*-fused ring junction is assigned to the heterorings (80JHC449). The stereochemistry of sulfoxides **46** and **47** was confirmed with the aid of a shift reagent (80JHC449). The axial position of the Br substituent in 6-bromo-2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-3,7-dione was indicated by the coupling constants between the 5- $\text{CH}_2$  protons and 6-H (72AJC1283).



## 7. Mass Spectrometry

The negative ion mass spectra of **21** was studied by an electron impact/Fourier transform ion cyclotron resonance mass spectrometry method (95MI13).

## 8. X-Ray Investigations

The structure of bis(pyrido[1,2,3-*de*]-1,4-benzothiazinium) dichloride (**44**, *n* = 0) was determined by an X-ray investigation (95SUL281).

# C. PYRIDO[1,2-*a*]PYRAZINES AND THEIR BENZO DERIVATIVES

## 1. Thermodynamic Aspects

The  $pK_a$  values of perhydropyrido[1,2-*a*]pyrazin-1-one, its 2-methyl derivative and their N-5 oxides were determined by potentiometric titration in a 4 : 1 mixture of 2-methoxyethanol and  $H_2O$  (81BAP423). The partition coefficients of 3-substituted 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]-quinolines have been determined in water–1-octanol [80IJC(B)879].

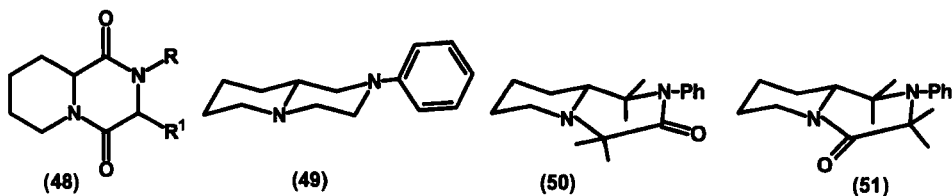
The purity of **24** (88MI10) and the physicochemical interactions of **24** with oxamniquine and tablet excipients (92MI7) were investigated with the aid of DSC. The solubility phase diagram of the praziquantel enantiomeric system was investigated (95MI9). Praziquantel was purified and its impurities were concentrated by directed sublimation [95KFZ(3)59, 95KFZ(6)45]. Dissolution properties of **24**– $\beta$ -cyclodextrin systems were investigated (96MI11).

## 2. Chromatographic Investigations

Praziquantel was determined quantitatively in biological fluids by means of HPLC (83MI1; 92MI5; 93MI2, 93MI5; 95MI2, 95MI3), and its enantiomers were resolved and investigated by chromatography (86MI1; 93MI3,

93MI15, 93MI18). Separation of praziquantel enantiomers was studied by chromatographic methods (95MI15, 95MI23; 96IEC169, 96MI4, 96MI6). Praziquantel was also investigated by GC (92MI24) and TLC (92MI6; 95MI17). Verruculotoxin (**23**) and its 9a-epimer were investigated by HPLC (87MI1, 87MI2). Enantiomers of 8-chloro-3-[(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl]-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline were separated by preparative HPLC (94MIP6).

Pyrolysis–gas chromatography was used to determine the degradation of peptides to diketopiperazines (among them Pip-Sar and *cis*- and *trans*-Val-Pip, like **48**) for sequence determination in actinomycins [71JCS(CC)39].



### 3. Theoretical Calculations

The electron densities, the bond orders, the first six energies and the oscillator strengths of the pyrido[1,2-*c*]pyrazinium cation were calculated by using the SCF-MO semiempirical version of the PPP method. Protonation is expected to take place on the nonbridgehead N atom, and position 1 is predicted to be the most reactive toward nucleophilic substitution (68TCA417). The minimum-energy conformations of 2-(*cis*-1,4-H-4-hydroxycyclohexylcarbonyl)-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrazino[2,1-*a*]-isoquinolin-2-one were calculated by the molecular mechanics program MMX [91AP(324)479]. Different properties of **24** and its analogs were calculated by MMP2 and MNDO methods (90MI4; 92MI15). A structure and activity relationship of antiparasitic **24** and its analogs was studied with different methods (93MI14; 94MI14). Electrochemical parameters were used to determine the possibility of resolving **24** into enantiomers via charge-transfer complexation on a chromatographic column [90DOK(312)1137]. The conformational analysis of **24** was performed using molecular mechanics (96MI5).

### 4. UV and CD Spectroscopy

The electronic absorption spectra of 2,3-diaryl-3,5,6,7-tetrahydropyrido[1,2,3-*de*]quinoxalines have been investigated (65JOC2589). Spectroscopic methods [colorimetric (89MI11; 92MI12), direct UV and difference UV, and IR [88KFZ(9)1140; 89URP1489777]] were developed for the quantita-

tive determination of **24**. 2-Benzoyl-1,2,3,6,7,11*b*-hexahydro- and 2-cyclohexylcarbonyl-1,2,3,11*b*-tetrahydro-4*H*-pyrazino-[2,1-*a*]isoquinolin-4-ones were identified in **24** as main impurities by UV, spectrophotometry, <sup>1</sup>H-NMR, and GC-mass spectra (89MI6).

The absolute configuration *R* was determined for (–)-1,2,3,4,6,7-hexahydro-11*bH*-pyrazino[2,1-*a*]isoquinoline in ORD and CD investigations (67CB1383). The *n*- $\pi^*$  Cotton effect of the 2-dithiocarbamate derivative of the (*S*)-enantiomer (69T725), and that of the 2-nitroso derivative of the (*R*)-enantiomer [71JPR(313)825] were measured. The *R*- and *S*-configurations were assigned to the (–) and (+) enantiomers of **24** respectively, on the basis of the CD spectra (85CB4620). The absolute configuration of veruculotoxin (**23**) was established by the analysis of its CD spectrum (76JA246). The structures of cyclodipeptides such as **48** containing pipecolic acid and other amino acids were studied by CD spectroscopy (72TL1437). The racemization of optically active 3-isopropylperhydropyrido[1,2-*a*]-pyrazine-1,4-dione was studied in 0.1*M* NaOH (73CCC3307).

### 5. IR Spectroscopy

The strong Bohlmann bands in the IR spectra of perhydropyrido[1,2-*a*]pyrazines and their 1-oxo- and 3-oxo derivatives indicate the predominance of the *trans*-fused ring conformation [60JOC2108; 69JHC181; 72JCS(P2)1374; 73CPB1248; 85BAP39; 93JOC690]. Replacement of the C-4 methylene hydrogens by deuterium atoms in 2-phenylperhydropyrido[1,2-*a*]pyrazine (**49**) causes the disappearance of the 2700 cm<sup>–1</sup> band, and is accompanied by a drop in intensity of the 2815 cm<sup>–1</sup> band and the appearance of a new band at 2785 cm<sup>–1</sup>. Replacement of the C-3 methylene hydrogens by deuterium atoms causes no alteration in the positions of the main bands and only small reductions in the intensities of the 2815, 2770, and 2860 cm<sup>–1</sup> bands [72JCS(P2)1374].

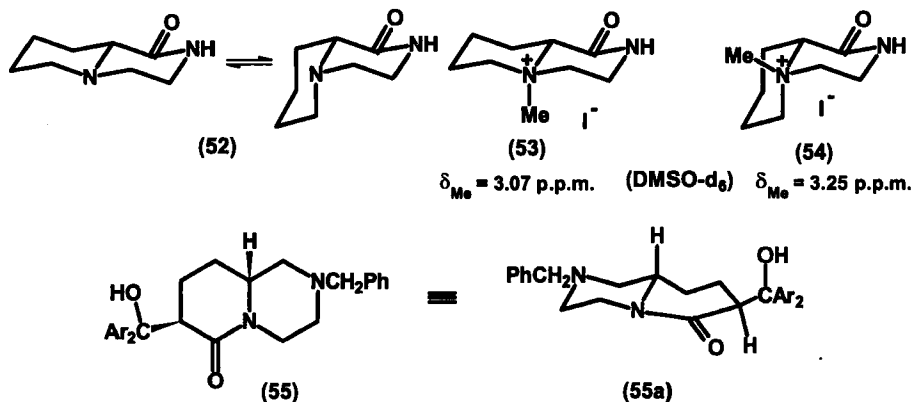
A *trans*-fused ring junction was identified for 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolines and their 1-oxo derivatives (75IJC230) and for 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrazino[2,1-*a*]isoquinolines (84JMC 995) on the basis of the appearance of Bohlmann bands in their IR spectra. The structures of cyclodipeptides **48**, derived from pipecolic acid and other amino acids, were studied by IR spectroscopy (72CCC4060, 72TL1437; 73CCC1957). An infrared spectrophotometric determination of **24** in CCl<sub>4</sub> was elaborated (91MI17).

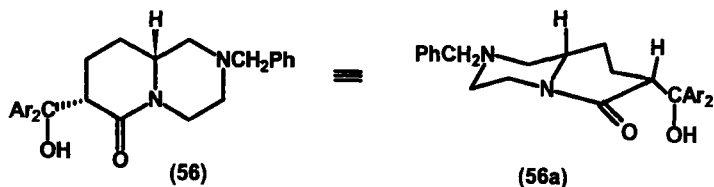
### 6. <sup>1</sup>H NMR Spectroscopy

2-Phenylperhydropyrido[1,2-*a*]pyrazine (**49**) and its 9-methyl-substituted derivatives adopt an all-chair *trans*-fused conformation in which the



phenyl group is at right angles to the plane of the perhydropyrazine ring, preventing conjugation between the  $\pi$ -electron system of the phenyl ring and the N lone pair of electrons [72JCS(P2)1374]. Thus, the effect on the  $J_{\text{gem}}$  value of the adjacent N-Ph group is small, and  $J_{\text{gem}}$  coupling constants of  $-11.7$  Hz and  $-11.1$  Hz were observed for the C-3 and C-1 methylene protons, respectively, i.e., these values were close to that of  $J_{4\text{eq},4\text{ax}}$  ( $-11.3$  Hz) in perhydroquinolizine. 2-Phenylperhydropyrido[1,2-*a*]pyrazin-3-one (**50**) and its 9-methyl derivative adopt a *trans*-fused ring conformation, with the piperidine ring in a chair conformation and the perhydropyrazine ring in a half-chair conformation, the lactam plane bisecting the C-4 methylene group [72JCS(P2)1374]. 2-Phenylperhydropyrido[1,2-*a*]pyrazin-4-one (**51**) and its 9-methyl derivative exist in a conformation in which the piperidine ring is likewise in a chair conformation and the perhydropyrazine ring is in a half-chair conformation, with the lactam plane bisecting the C-3 methylene group and 6- $\text{H}_{\text{eq}}$  lying in the lactam plane. For these two perhydropyrido[1,2-*a*]pyrazinones, the magnitude of  $J_{\text{gem}}$  for the methylene group protons adjacent to the lactam N depends on the orientation of the lactam carbonyl group with respect to the methylene group [72JCS(P2)1374]. It was concluded that perhydropyrido[1,2-*a*]pyrazin-1-one (**52**) exists as a mixture of *trans*-fused and *cis*-fused conformers, as it reacted with MeI in MeOH to give a 1 : 1.5 mixture of methiodides **53** and **54** (73CPB1248). Conformational analysis of perhydropyrido[1,2-*a*]pyrazin-6-ones (**55**) and (**56**) indicated a *trans*-fused and a *cis*-fused ring conformation, respectively, in which the bulky diarylhydroxymethyl group was in the equatorial orientation (93JOC690). Both C-7 epimers of 2-substituted 7-(diarylmethyl)perhydropyrido[1,2-*a*]pyrazine exist in *trans*-fused all-chair ring conformations; the 7-substituent in the *cis*-7,9*a*-H epimer is in the axial position, while that in the *trans*-7,9*a*-H epimer is in the equatorial position.





Conformational analysis of cyclodipeptides (diketopiperazines) **48**, derived from D and L-pipecolic acids and glycine, sarcosine, and other  $\alpha$ -amino acids, demonstrates that the magnitude of  $^3J_{\text{NHCH}}$  is a measure of the buckled conformation of the diketopiperazine ring, assuming a Karplus-type dependence with Q(HNCH) and a planar peptide bond [73CCC1940; 76JCS(P2)187; 80BSB615; 85BSB413]. A correlation is observed between  $^3J_{\text{NHCH}}$  and  $^5J_{\text{H,H}}$  for a number of cyclodipeptides, which indicates that  $^5J_{\text{H,H}}$  depends on the conformation of the diketopiperazine ring. The diketopiperazine ring of cyclo-D-Pip-X (X = Gly, Leu, or Phe) has been shown to exist in an approximately planar conformation, with the 6 membered D-Pip ring in a chair conformation.

The two epimers of 7-aryl-2,3,4,8,9,9a-1*H*-, and 2,3,4,6,9,9a-1*H*-hexahydro-, and 7-arylhydropyrido[1,2-*a*]pyrimidines adopt a *trans*-fused half-chair-chair and a chair-chair conformation, respectively (94T1811). The structures of 2-cyclohexylcarbonyl-1,2,3,6,7,11*b*-hexahydro- and 2,3,6,7-tetrahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones were determined by means of  $^1\text{H}$  NMR spectroscopy [91KFZ(9)85]. The  $^1\text{H}$  NMR was used for quantitative determination of **24** in pharmaceutical preparation (90SPL505; 95MI12). The two large coupling constants (12.0 Hz and 9.0 Hz) of 4a-H justified a *trans*-fused ring conformation for 9-trifluoromethyl-2,3,4,4a,5,6-hexahydropyrazino-[1,2-*a*]quinoline (85JMC945). The structure of 3-[(4-hydroxyphenyl)methyl]-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione was investigated and determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy (93MI22; 95MI6).

Contrary to an earlier suggestion (72JMC351), the  $^1\text{H}$  NMR chemical shift of the 4a-H of 2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines is not a suitable criterion for the presence of a *trans*-fused or a *cis*-fused conformation [94JCR(S)346].

## 7. $^{13}\text{C}$ NMR Spectroscopy

Perhydropyrido[1,2-*a*]pyrazin-1-one (**52**), its protonated form, its *trans*- and *cis*-fused N-oxides and its methiodides (85BAP39; 88PJC709), and 2-methylperhydropyrido-[1,2-*a*]-pyrazin-1-one and its *trans*- and *cis*-fused N-oxides (85BAP39) have been investigated by  $^{13}\text{C}$  NMR spectroscopy.

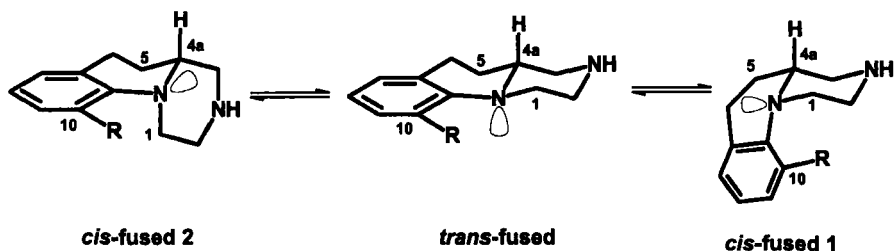
$^{13}\text{C}$  NMR data on different 2-acyl-1,2,3,6,7,11*b*-hexahydro- and 2,3,6,7-tetrahydro-4*H*-pyrazino[2,1-*a*]isoquinolines were determined in  $^1\text{H}$ - $^{13}\text{C}$ -heterocorrelation 2D-NMR experiments [89AP(322)795]. The structures of 2-acyl-1,2,3,6,7,11*b*-hexahydro- and 2,3,6,7-tetrahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones were similarly characterized by  $^{13}\text{C}$  NMR [89AP(322)795; 91KFZ(9)85].  $^{13}\text{C}$  NMR investigations revealed that whereas 10-unsubstituted 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines adopted a *trans*-fused conformation (Scheme 5), 10-methyl derivatives existed in the *cis*-fused 2-conformation, this being the most favored because it maximizes the distance between the methyl and the C-1 methylene groups [94JCR(S)346]. In this conformation 5-C is involved in two  $\gamma_{\text{gauche}}$  effects with the C-1 and N-3 groups ( $^{13}\text{C}$  chemical shift of 5-C: R = H, 27.1 ppm, versus R = Me, 20.3 ppm in  $\text{CDCl}_3$ ).

### 8. Mass Spectroscopy

The electron impact mass spectra of 2-acyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino-[2,1-*a*]isoquinolin-4-ones have been studied (91OMS503). 1,3,4,6,11,11*a*-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline metabolites of quinapril were determined in biological fluids by means of GC-mass spectrometry (92MI4). Hydroxylated metabolites of **24** were characterized by tandem mass spectrometry (90AF1159, 90MI5, 90MI6; 96MI7). 2-(1-Butyl)perhydropyrido[1,2-*a*]pyrazine was identified as a by-product in the reaction mixture of diquat, reduced with  $\text{NaBH}_4$ - $\text{NiCl}_2$ , by GLC-mass spectrometry (91CPB956). Flow-injection-mass spectrometry was used to monitor the reaction of *cis*-7,9*a*-H-2-(2-pyrimidinyl)-7-(2,5-dioxo-pyrrolidinomethyl)perhydropyrido[1,2-*a*]pyrazine (96TAL851).

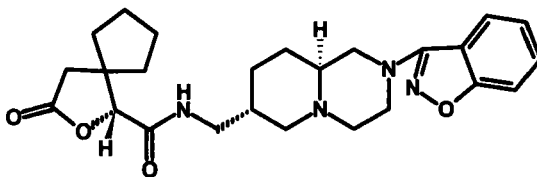
### 9. X-Ray Investigations

The solid-state structures of (3*R*,9*aS*)-3-benzyl-2-methyl- (82BSB213), (3*S*,9*aR*)-3-isobutyl- [87AX(C)1603], (3*S*,9*aS*)-3-isopropyl- [91AX(B)92],



SCHEME 5

and (3*R*,9*aR*)-3,4-dimethylperhydropyrido[1,2-*a*]pyrazine-1,4-dione [93AX(C)1113], (9*aS*)-2,3,4,6,9,9*a*-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-1,4-dione monohydrate [83AX(C)905], and 3-[(4-hydroxyphenyl)methyl]-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (95MI6) were determined in X-ray investigations. The stereostructure of veruculotoxin (**23**) was determined by X-ray diffraction analysis (76JA246). The absolute configuration of perhydropyrido[1,2-*a*]pyrazine **57** was determined by X-ray analysis (94TA211). X-ray analysis of the L-tartaric acid salt of (+)-*cis*-7,11*b*-H-2-methyl-7-phenyl-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrazino[2,1-*a*]isoquinoline confirmed its conformation and established the absolute configuration at asymmetric C-7 and C-11*b* as *S,S* [84AX(C)1103, 84JMC995]. The solid-state structures of 2-(*cis*-1,4-H-4-hydroxycyclohexylcarbonyl)- [91AP(324)479], and 2-(3- and 4-nitrobenzoyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones were determined by means of X-ray analysis [91AX(C)2492; 92AX(C)1868].



(57)

Two crystal modifications and an amorphous phase were found for **24** by X-ray diffraction and differential thermogravimetric analysis [91KFZ(3)78]. The structure of a complex formed from 3-[*p*-methylphenyl]amino]-4-[(*p*-methylphenyl)imino]-4*H*-pyrido[1,2-*a*]pyrazine, sodium bis(trimethylsilyl)amide and (norbornadiene)Mo(CO)<sub>4</sub> in THF was characterized by single-crystal X-ray diffraction [95JPR(337)38].

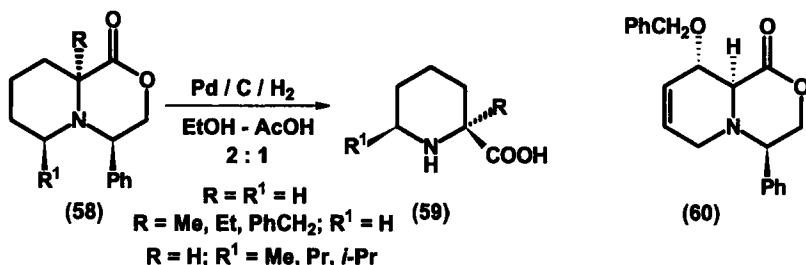
### III. Reactivity

#### A. PYRIDO[2,1-*b*][1,4]OXAZINES AND THEIR BENZO DERIVATIVES

##### 1. Ring Opening

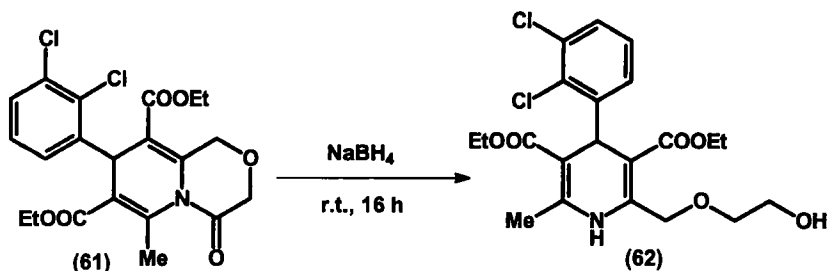
Treatment of 6-methylperhydropyrido[2,1-*b*][1,4]oxazin-1-one with lithium aluminum hydride (LAH) in Et<sub>2</sub>O gave the ring-opened 1-(2-hydroxyethyl)-2-hydroxymethyl-6-methylpiperidine (66JMC311; 68USP 3388128). 2-Hydroxymethyl-1-(2-aryl-2-hydroxyethyl)piperidines were obtained from 3-aryl-3-hydroxyperhydropyrido[2,1-*b*][1,4]oxazines by catalytic reduction over Pd-C or Pd(OH)<sub>2</sub>-C, or by treatment with NaBH<sub>4</sub>

(76JMC334; 78JMC460). Reductive ring cleavage of 3,7,8,9-tetrahydroxyperhydropyrido[2,1-*a*][1,4]oxazines with  $\text{NaBH}_4$  afforded 1-(hydroxyethyl)-2-hydroxymethyl-3,4,5-trihydropiperidines (91GEP3936295). Hydrogenation of optically active 4-phenylperhydropyrido[2,1-*c*][1,4]oxazines (**58**) over 10% Pd-C in a 2 : 1 mixture of EtOH and AcOH afforded (*S*)-(-)-pipecolic acid and its 2- and 6-derivatives (**59**) (94JOC3769). Pyrido[2,1-*c*][1,4]oxazine **60** in EtOH over  $\text{Pd}(\text{OH})_2$  yielded (2*S*,3*S*)-3-hydroxypipelic acid (96TL4001). Hydrogenation of 4*c*,9*at*-H-1,4-*cis*-diphenyl-1-hydroxyperhydropyrido[2,1-*c*][1,4]oxazine over  $\text{PtO}_2$  in acidified MeOH gave *erythro*-2-[phenyl(hydroxy)methyl]-1-(1-phenyl-2-hydroxyethylpiperidine) (88SC823). Treatment of pyrido[2,1-*c*][1,4]oxazine **61** with  $\text{NaBH}_4$  in EtOH yielded 1,4-dihydropyridine **62** (85EUP161917, 85EUP164247; 91JMC19). Reduction of 1-substituted 4-phenylpyrido[2,1-*c*][1,4]oxazines **63** with LAH gave aminoalcohols **64** (96JOC6700).

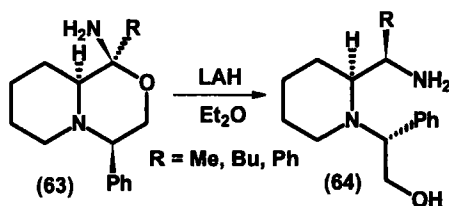


Treatment of 6,8-diphenyl-3-methyl-1-oxopyrido[2,1-*b*][1,4]oxazinium tetrafluoroborate with *tert*-BuNH<sub>2</sub> in THF furnished 1-propenyl-2,4-diphenylpyridinium tetrafluoroborate [82CS(20)147]. Reaction of 1-methylperhydropyrido[2,1-*c*][1,4]oxazin-3-one with PhNHNH<sub>2</sub> gave 2-[2-(1-hydroxyethyl)piperido]acetic phenylhydrazide [61AP(294)468]. Cleavage of 4-phenyl-8-substituted perhydropyrido[2,1-*c*][1,4]oxazin-1-ones with vinyl chloroformate followed by acidic hydrolysis yielded 4-substituted pipecolic acids (90SL731; 92T431). Similarly, 1-oxo-4-phenyl-7*a*-hydroxyperhydro[1,4]oxazino[3,4-*a*]isoquinoline gave methyl 4*a*-hydroxyperhydroisoquinoline-1-carboxylate (92T431). Treatment of 3,7-dihydro- and 6-bromo-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-diones with amines or alcohol led to (4-hydroxy-8-quinolyl)acetamides or acetates, respectively [70CR(C)498, 70CR(C)1189].

Hydrolysis of dimethyl 6-methyl-8-(3-nitrophenyl)-3-oxo-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazine-7,9-dicarboxylate in MeOH in the presence of KOH at room temperature afforded 2-[2-hydroxymethyl-6-methyl-4-(3-nitrophenyl)-3,5-bis(methoxycarbonyl)-1,4-dihydropyridin-1-yl]acetic acid (95PHA681). Hydrolysis of 7,8,9,10-tetrafluoro-1,2,4,6-tetrahydro[1,4]ox-



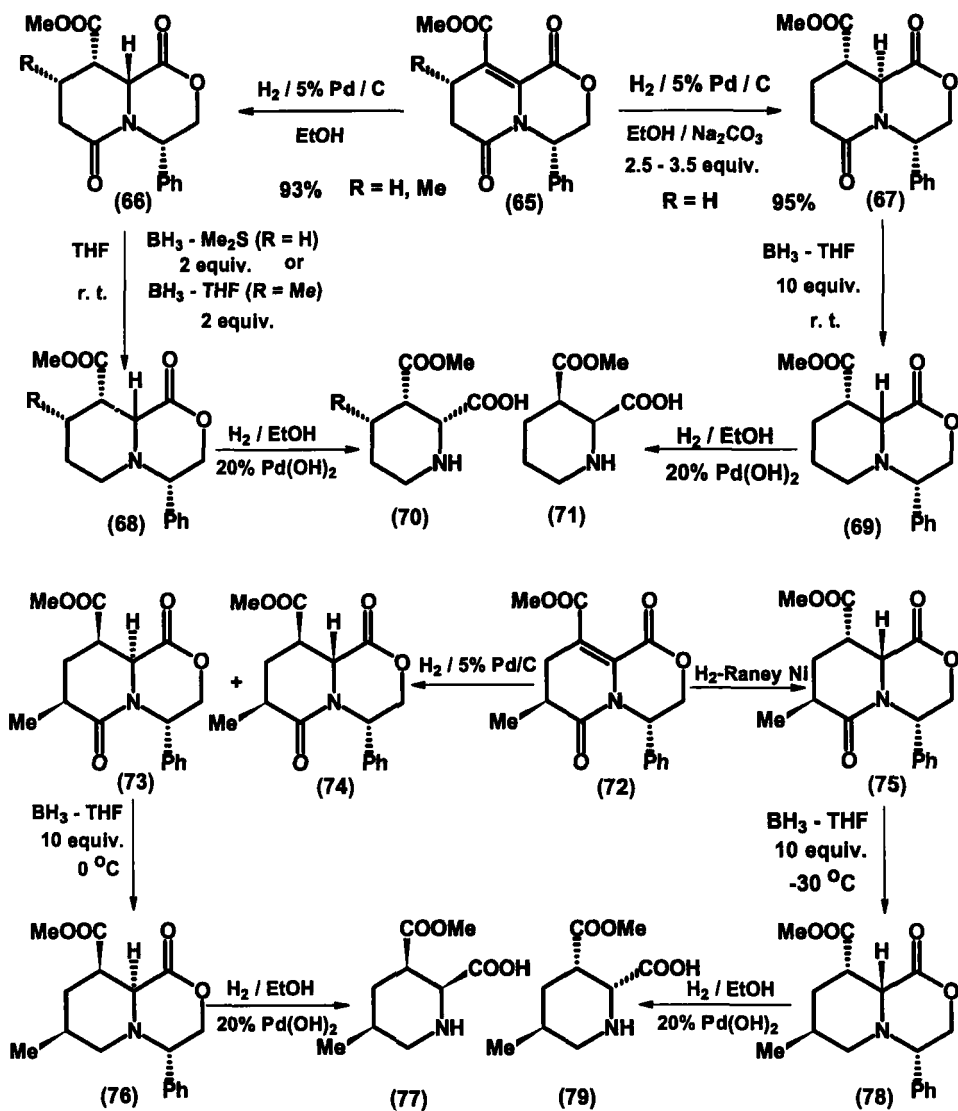
azino[4,3-*a*]quinoline-4,6-dione with aqueous KOH gave potassium 1-(2-hydroxyethyl)-5,6,7,8-tetrafluoro-4-oxoquinoline-2-carboxylate (94IZV299, 94JFC119). Acidic hydrolysis of a diastereomeric mixture of 3-ethyl-3-methyl-1,3,4,6,11,11*b*(*S*)-hexahydro[1,4]oxazino[4,3-*b*]isoquinoline-1,4-diones afforded (*R*)-2-hydroxy-2-methylbutyric acid with 64% optical purity (77CL1109; 79T2345).



## 2. Reduction, Hydrogenation

Perhydropyrido[2,1-*c*][1,4]oxazines were obtained from perhydropyrido[2,1-*c*][1,4]oxazin-4-ones by reduction with LAH [57N584; 60AP(293)74; 63AP(296)38; 72JCS(P2)1374; 81EUP34015; 92BMC523] and with  $\text{BH}_3$  (88EUP279707). When  $\text{LiAlD}_4$  was applied, 4,4-dideuterio derivatives of perhydropyrido[2,1-*c*][1,4]oxazines were obtained [72JCS(P2)1374, 72OMR(4)283].

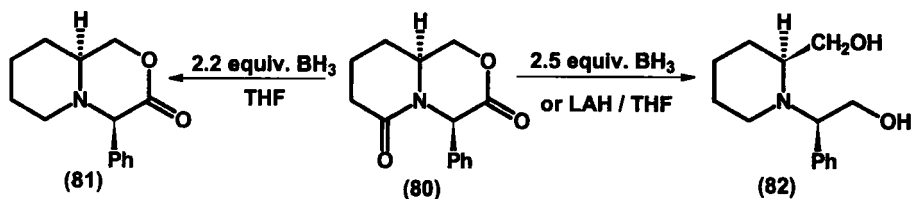
Catalytic hydrogenation of 1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-1,6-diones (**65**) over 5% Pd-C gave perhydro derivatives **66** (95TL1657; 96JOC5736). The stereoselectivity of the reduction was governed by steric factors. Similar reduction of **72** afforded a 4 : 1 mixture of **73** and **74** (96JOC5736). When **65** ( $\text{R} = \text{H}$ ) was reduced in the presence of  $\text{Na}_2\text{CO}_3$  or **72** was reduced over Raney Ni, 9*a*-epimer **67** and diastereomer **75**, respectively, were the products. Reduction of the amido moiety of perhydropyrido[2,1-*c*][1,4]oxazine-1,6-diones **66**, **67**, **73**, and **75** gave perhydropyrido[2,1-*c*][1,4]oxazin-1-ones **68**, **69**, **76**, and **78**. Hydrogenation of compounds **68**, **69**, **76**, and **78** over  $\text{Pd}(\text{OH})_2$  and subsequent saponification



SCHEME 6

of the lactone moiety afforded optically active half-esters of 2,3-piperidinedicarboxylic acids **70**, **71**, **77**, and **79** (Scheme 6).

Reduction of *cis*-4,9a-H-4-phenylperhydropyrido[2,1-c][1,4]oxazine-3,6-dione (**80**) with 2.2 eq  $BF_3$  in THF yielded the 3-oxo derivative **81** [95H(41)1931]. When 2.5 eq of  $BF_3$  or LAH were applied, ring-opened **82** was obtained. Reduction of 8- and 9-hydroxyiminoperhydropyrido[2,1-



*c*][1,4]oxazines by treatment with sodium in boiling amyl alcohol afforded *cis*-8,9*a*-H-8-amino- and *trans*-9,9*a*-9-aminoperhydro derivatives, respectively (81EUP34015; 82EUP57536). Reduction of 3,4,7,8,9-pentahydroxyperhydropyrido[2,1-*c*][1,4]oxazines over 10% Pd-C at 60°C under hydrogen pressure (50 bar) in H<sub>2</sub>O or with NaBH<sub>4</sub> in water at pH 5.0–5.5 gave 3,7,8,9-tetrahydroxy derivatives (91GEP3936295). 1,3,4,6,7,11*b*-Hexahydro[1,4]oxazino[3,4-*a*]isoquinoline was prepared from 1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinolin-4-one and -6-one with LAH, from a 7-oxo derivative by Clemmensen reduction, and from a 7-hydroxy derivative and 1,3,4,11*b*-tetrahydro[1,4]oxazino[3,4-*a*]isoquinoline by catalytic reduction over Pd-C (67BRP1094470, 67NEP6611733). The 7-hydroxy derivative of 1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline was obtained from its 7-oxo derivative with NaBH<sub>4</sub>. 1,3,4,6,7,11*b*-Hexahydro[1,4]oxazino[3,4-*a*]isoquinolines were obtained from 3,4,6,7-tetrahydro[1,4]oxazino[3,4-*a*]isoquinolinium chlorides by reduction with NaBH<sub>4</sub> (67BRP1094470, 67NEP6611733; 68SAP68/02790). 1,2,4,4*a*,5,6-Hexahydro[1,4]oxazino[4,3-*a*]quinoline was prepared by reduction of its 1-oxo derivative with LAH (72IJC1134). Catalytic reduction of 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine over PtO<sub>2</sub> in AcOH gave perhydropyrido[1,2,3-*de*]-1,4-benzoxazine (44HCA1756). 3,5,6,7-Tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-diones [69CR(C)564; 70CR(C)498] or 7-hydroxy-6-ethoxycarbonyl-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one derivatives [70CR(C)498] over 5% Pd-C in AcOH yielded 3,4,5,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-ones. Treatment of 9-fluoro-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione in CF<sub>3</sub>COOH with Et<sub>3</sub>SiH gave a 3-one derivative (89EUP406993). The 3-oxo group was reduced to a methylene group with LAH [69CR(C)564]. Catalytic reduction of 3-ethoxycarbonylmethylene-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-2-one over 10% Pd-C in EtOAc gave a 3-ethoxycarbonylmethyl-3,5,6,7-tetrahydro derivative [79PIA(A)1]. 7-Amino-3,4,5,6-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one was obtained from the 7-hydroxyimine derivative, prepared from 3,4,5,6-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione and H<sub>2</sub>NOH, by catalytic hydrogenation over PtO<sub>2</sub> in AcOH



[69CR(C)564]. Reduction of 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-diones with alkaline borohydride [70CR(C)498; 72AJC1283; 89EUP406993] or over Raney Ni [69CR(C)564; 70CR(C)498] afforded the corresponding 7-hydroxy-3-one derivative. Catalytic reduction of ethyl 9,10-difluoro-3-methylene-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate over 5% Pd-C in ethanol at room temperature yielded the 3-methyl derivative (91CCC1937). Catalytic reduction of a mixture of 3,10-dimethyl-3,5- and -3,7-dihydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines over Rh-Al<sub>2</sub>O<sub>3</sub> in THF yielded a 3,5,6,7-tetrahydro derivative (88GEP3817565; 90GEP3936250).

### 3. Reactivity of Rings

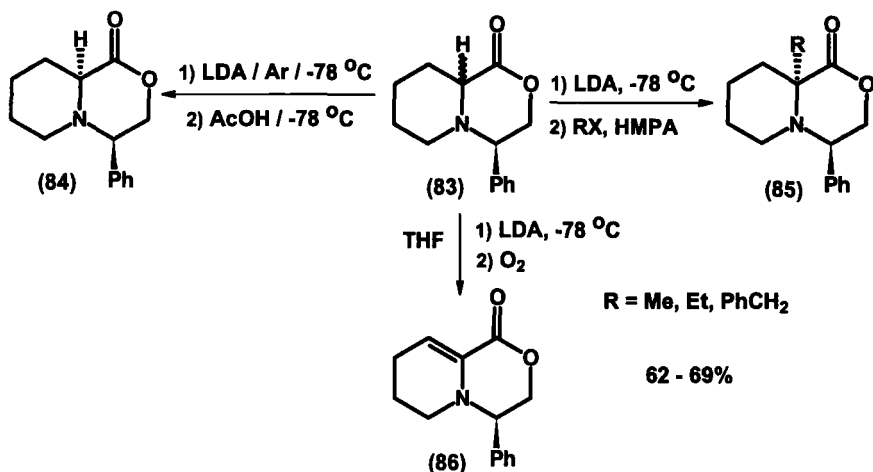
Methiodide and ethiodide salts were prepared from perhydropyrido[2,1-*c*][1,4]oxazines [58N516; 60AP(293)74; 63AP(296)38], from 1,3,4,6,7,11*b*-hexahydro-[1,4]oxazino[3,4-*a*]isoquinolines (67BRP1094470, 67NEP 6611733; 85AJC1591), and from perhydropyrido[1,2,3-*de*]-1,4-benzoxazine (44HCA1756) with alkyl iodides.

The 8-bromo atom of 8-bromo-1-hydroxy- and 8-bromo-1-silyloxy-4-phenylperhydropyrido[2,1-*c*][1,4]oxazines was replaced by an acetoxy group on treatment with CsOAc (90SL731; 92T431), by a phenylthio group with PhSH in the presence of ZnCl<sub>2</sub>, or by an azide group with NaN<sub>3</sub> (92T431).

Oxidation of 8,9-dihydroxy-1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinolin-1-one with SeO<sub>2</sub> in hot AcOH afforded 8,9-dihydroxy-1-oxo-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*b*]isoquinolinium chloride (85MI2).

Epimerization of methyl 4-phenyl-1,6-dioxoperhydropyrido[2,1-*c*][1,4]oxazine-9-carboxylate (**66**, R = H) to **67** occurred smoothly in abs. EtOH in the presence of Na<sub>2</sub>CO<sub>3</sub> at room temperature (96JOC5736). A mixture of *cis*- and *trans*-3,11*b*-H-3-carboxy- and -3-cyano-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline was converted to the more stable *trans* acid, containing an equatorial carboxy group, on prolonged treatment with base (78JMC785). Treatment of a 70 : 30 mixture of (*9aS*) and (*9aR*)-4-phenylperhydropyrido[2,1-*c*][1,4]oxazin-4-ones (**83**) with LDA in THF at -78°C under argon, followed by addition of AcOH gave pure (*9aS*)-derivative **84** (94JOC3769). When hexamethylphosphoric triamide (HMPA; 2 eq) and alkyl iodides and PhCH<sub>2</sub>Br were also added to the reaction mixture after lithium diisopropylamide (LDA), 9*a*-substituted derivatives **85** were obtained. 4-Phenyl-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazin-4-one (**86**) was prepared by bubbling O<sub>2</sub> at -78°C for 1 minute into a THF solution of the enolate, prepared from an epimeric mixture of 4-phenylperhydropyrido[2,1-*c*]-[1,4]oxazin-1-one with LDA (94JOC3769).

Reductive radical decyanation of 5,5-dicyano-1,2,4,4*a*,5,6-hexahydro-[1,4]oxazino[4,3-*a*]quinoline with a mixture of Bu<sub>3</sub>SnH and 2,2'-azobisisobutyronitrile afforded nearly a 1 : 1 mixture of diastereomers of its 5-cyano derivative (95TL5159).

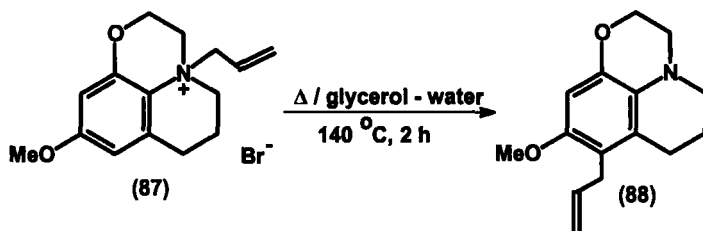


Reaction of 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione with diethyl carbonate or diethyl oxalate in the presence of *tert*-BuOK gave 6-ethoxycarbonyl and 6-ethoxalyl derivatives, respectively [70CR(C)498]. The 6-ethoxycarbonyl derivative was also obtained by decarbonylation of the 6-(ethoxycarbonyl)carbonyl derivative at 180°C [70CR(C)498]. The reaction of a 6-ethoxycarbonyl-2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione derivative with PhNHNH<sub>2</sub> yielded the appropriate tetracyclic pyrazolo derivative [70CR(C)498]. 7-Acyl derivatives were prepared from 2,5,6,7-tetrahydro-3*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one with acyl chlorides in the presence of AlCl<sub>3</sub> [70CR(C)498]. Leuckart-Wallach reaction of 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione furnished the 7-formylamino derivative [69CR(C)564]. 8-Acyl-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-ones were prepared from the parent 8-unsubstituted derivative with acyl chloride in the presence of AlCl<sub>3</sub> [70CR(C)498]. The hydroxy group of 7-hydroxy-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one was acylated with Ac<sub>2</sub>O, and converted into the 7-chloro derivative in conc. HCl at 20°C [69CR(C)564]. Pyrolysis of the 7-acetoxy derivative in the presence of KHSO<sub>4</sub> at 210°C afforded 3,5-dihydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one. A 3,5-dihydro derivative was also obtained from 9-fluoro-7-hydroxy-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one on heating in toluene in the

presence of *p*-toluenesulfonic acid (*p*-TSA) (89EUP406993). 7-Amino derivatives were obtained from the 7-chloro derivative by reaction with aliphatic and alicyclic amines [69CR(C)564]. Reaction of 2,3-dihydro-7-hydroxy-9-methoxy-6-(1-indolinylcarbonyl)-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one with POCl<sub>3</sub> at 80°C afforded the 7-chloro derivative (93MIP4). The 7-chloro atom was changed for an amino group with NH<sub>3</sub> in a mixture of EtOH and CHCl<sub>3</sub> at 100°C in a sealed tube.

Treatment of 6-bromo-2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione with NEt<sub>3</sub> yielded 2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione [70CR(C)1189]. Distillation of 6-hydroxy-3,10-dimethyl-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine from solid KOH gave approximately a 1 : 1 mixture of 3,5- and 3,7-dihydro-2*H* derivatives (88GEP3817565; 90GEP3936250).

N-Claisen rearrangement of the quaternary salt **87** afforded the 8-allyl derivative **88** with a few percent of the deallylated product [86JCS(CC)1308].

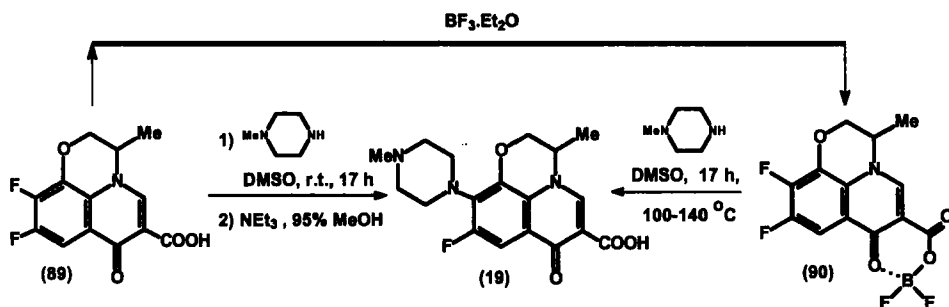


Bromination of 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine with *N*-bromosuccinide (NBS) gave the 9-bromo derivative, which was converted to the 9-methoxy derivative with NaOMe in the presence of CuI [86JCS(CC)1308]. Depending on the molar ratio, 6-bromo or 6,6-dibromo derivatives were prepared from 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione with Br<sub>2</sub> [70CR(C)498; 72AJC1283]. Electrophilic reactions of 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-ones with 66% HNO<sub>3</sub> in a mixture of AcOH and Ac<sub>2</sub>O; with conc. HNO<sub>3</sub> and NaNO<sub>2</sub> in AcOH in the presence of Ac<sub>2</sub>O and *p*-TSA; with Br<sub>2</sub>, ICl, and AcCl in the presence of AlCl<sub>3</sub> in PhNO<sub>2</sub>; with *tert*-BuOH in conc. H<sub>2</sub>SO<sub>4</sub>; and with *i*-PrBr in the presence of AlCl<sub>3</sub> in PhNO<sub>2</sub> afforded 9-nitro (84GEP3234529), 8,9-dinitro [92PIA(A) 549], 8-nitroso (84GEP3234529), 8-bromo [84GEP3234529; 92(PIA(A) 549], 8-iodo, 8-acetyl, 8-*tert*-butyl, and 8,10-diisopropyl derivatives (84GEP3234529), respectively. Nitration of 9-fluoro-2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one afforded an 8-nitro derivative (89EUP406993). Nitration of 3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid and its 10-phenyl de-

rivative with 70%  $\text{HNO}_3$  in conc.  $\text{H}_2\text{SO}_4$  or with 90%  $\text{HNO}_3$  afforded 8-nitro (75USP3883522; 76USP3984548) and 8-nitro-10-(*p*-nitrophenyl) derivatives (84USP4443447), respectively. Nitration of a 9,10-difluoro derivative in conc.  $\text{H}_2\text{SO}_4$  with  $\text{KNO}_3$  afforded an 8-nitro derivative (91JMC1142). Diazonium coupling of 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines with aryl diazonium salts occurred at position 9 (48USP2448869; 88GEP3817565; 90GEP3936250, 90GEP3940081).

The 9,10-difluoro-, 8,9,10-trifluoro-, 9-chloro-10-fluoro- and 10-fluoro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids and their 2,3-dihydro derivatives could be regioselectively substituted by cyclic amines at position 10 [82EUP47005, 82JAP(K)82/88182, 82JAP(K)82/88183, 82JAP(K)82/149286; 83JAP(K)83/52290, 83JAP(K)83/72588, 83JAP(K)83/72589, 83JAP(K)83/225092; 84CPB4907, 84EUP101829, 84EUP106489, 84JAP(K)84/01489, 84JAP(K)84/219293, 84USP4473568; 85EUP153163, 85EUP159174, 85JAP(K)85/34968, 85JAP(K)85/64984; 86AAC163, 86EUP172651, 86EUP206283, 86JAP(K)86/204188, 86JAP(K)86/271292; 87CPB1896, 87EUP208210, 87EUP215650, 87EUP228661, 87GEP3522405, 87GEP3522406, 87GEP3543513, 87GEP3601567, 87JAP(K)87/36383, 87JAP(K)87/155282, 87JMC2283; 88EUP265230, 88EUP287951, 88GEP3623757, 88GEP3641312, 88GEP3711193, 88JAP(K)88/60990, 88JMC983, 88JMC1694, 88JMC2004, 88USP4775668, 88USP4777253; 89EUP321191, 89EUP324298, 89EUP343524, 89EUP343560, 89JAP(K)89/09992; 90EUP368410, 90EUP388298, 90GEP3906365, 90JHC1509, 90JMC2270, 90MI8, 90MIP2; 91CCC1937, 91CCC2406, 91EUP413455, 91EUP424851, 91EUP424852, 91EUP429304, 91JAP(K)91/279361, 91JHC1061, 91JHC1067, 91JMC1142, 91MI1, 91USP5037834, 91USP5051505; 92CCC216, 92GEP4120646, 92JMC611, 92MI11, 92MIP2-92MIP4, 92USP5097032, 92USP5164402; 93EUP549857, 93EUP550016, 93EUP550019, 93EUP550903, 93EUP563732, 93EUP563733, 93EUP563734, 93EUP572259, 93JMC801, 93JMC1356, 93MIP3, 93MIP6; 94CPB1442, 94EUP589318, 94EUP591808, 94EUP614664, 94GEP4230804, 94GEP4234330, 94MIP1, 94MIP3, 94MIP5; 95JAP(K)95/300472, 95JMC1203, 95MIP3; 96EUP705828, 96MIP5, 96USP5539110]. As an N-nucleophile  $\text{MeNHNH}_2$  and  $\text{Me}_2\text{NH}$  were also applied (82EUP47005). The regioselectivity is changed if a nitro group is present in position 8. Reaction of 9,10-difluoro-3-methyl-8-nitro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid with  $(\text{NH}_4)_2\text{CO}_3$  yielded the 9-amino-10-fluoro-8-nitro derivative (96CPB987). The chloro atom of 10-chloro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid did not react, but the reaction of 9-fluoro-10-chloro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid with piperazine gave the 9-piperazino-10-chloro derivative (84CPB4907). Reaction of the 9,10-dichloro derivative with

cyclic amines occurred regioselectively at position 10 [82JAP(K)82/188592; 84CPB4907]. 9,10-Difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids [e.g., **89**] reacted with a cyclic amine above 100°C in a solvent (84CPB4907), whereas if a boron chelate, e.g., **90**, was used, then the reaction occurred smoothly [83JAP(K)83/210092; 87ABC1265; 95MIP4] even at room temperature [83JAP(K)83/43977; 85JAP(K)85/75489, 85JAP(K)85/78986; 86EUP206283; 87CPB1896; 88EUP273399; 90EUP354453, 90EUP357047, 90EUP368410; 91JAP(K)91/72476, 91MI13; 92EUP488227]. Reaction of 9,10-difluoro-3-methyl-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate with 1-*tert*-butoxycarbonyl-3-hydroxypyrrolidine and ethyl cyanoacetate in the presence of 60% NaH in DMF at 50°C afforded 10-(1-*tert*-butoxycarbonyl-3-pyrrolidinyloxy) (90EUP390215) and 10-cyano(ethoxycarbonyl)methyl derivatives [96JAP(K)96/41070], respectively.



The 10-bromo or chloro atom of 10-bromo-9-fluoro- and 10-chloro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates was substituted for a (het)aryl group with derivatives of 4-(tributylstannyl)pyridine in the presence of PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> (89EUP306860; 93BMC1711; 94USP5308843) or with PhLi in the presence of ZnCl<sub>2</sub> and (Ph<sub>3</sub>P)<sub>2</sub>NiCl<sub>2</sub> (86EUP184384). The 10-fluoro group of 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate was substituted for an azido group with NaN<sub>3</sub> (89EUP306860). Reaction of 8,9-difluoro-10-(2,6-dimethyl-4-pyridyl)-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate with PhCH<sub>2</sub>SH afforded the 8-benzylthio derivative, and the benzylthio group was eliminated by treatment with Raney Ni in boiling EtOH to give an 8-unsubstituted derivative (89EUP306860). Reaction of 10-(1-benzyloxycarbonylamino)cyclopropyl)-8,9-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid with PhCH<sub>2</sub>NH<sub>2</sub> and PhCH<sub>2</sub>OH in the presence of NaH afforded 8-benzylamino and 8-benzyloxy derivatives, respectively (89GEP3913245; 94CPB2063). Hydrogenation of the 8-benzylamino and 8-

benzyloxy derivatives over 5% Pd-C in AcOH gave 8-amino and 8-hydroxy derivatives (94CPB2063).

Heating 10-(4-methyl-1-piperazinyl) and 10-fluoro-substituted derivatives of ethyl 9-fluoro-3-methylene-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate in a 1 : 1 mixture of conc. HCl and AcOH afforded 3-hydroxy-3-methyl-6-carboxylic acid derivatives (92CCC216).

3-Alkoxy-3-phenylperhydropyrido[2,1-*c*][1,4]oxazines were formed from the 3-hydroxy derivative **25** (R = OH) in boiling alcohols via an intermediate carbenium-oxonium ion, stabilized by the 3-phenyl group [78JMC460; 90AP(323)53].

#### 4. Reactivity of Substituents Attached to Ring Carbon Atoms

The ester group of [1,4]oxazino[4,3-*a*]quinolinecarboxylates (80JHC 1729) and 7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates [70 CR(C)498; 75USP3883522; 76USP3984548; 82EUP47005; 83JAP (K)83/52290, 83JAP(K)83/72588; 84CPB4907, 84EUP101829, 84JAP(K) 84/01489, 84USP4443447; 86AAC163, 86CPB4098, 86EUP184384, 86 EUP206283, 86JAP(K)86/204188; 87ABC1265, 87CPB1896, 87GEP 3522405, 87GEP3543513; 88EUP273399, 88GEP3623757, 88GEP3711193, 88JAP(K)88/60990, 88JMC1694, 88JMC2004, 88USP4777253; 89EUP 306860, 89GEP3913245, 89JAP(K)89/09992, 89MI5; 90EUP368410, 90 JHC1509, 90MI8, 90MIP2; 91CCC1937, 91JHC1061, 91JHC1067; 92 CCC216; 93BMC1711, 93EUP563732-93EUP563734, 93MIP8; 94CPB2063, 94CPB2569, 94CPB2629, 94MIP3, 94USP5308843; 96MIP1] was hydrolyzed under basic or acidic aqueous conditions. The carboxylic group was liberated from a borate complex by treatment with NEt<sub>3</sub> in MeOH (94CPB1442). Hydrolysis of diethyl [(9,10-difluoro-6-ethoxycarbonyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-yl)methyl]malonate in a mixture of aqueous AcOH and H<sub>2</sub>SO<sub>4</sub> under reflux gave a 3-substituted propionic acid derivative (93EUP563734). Ofloxacin (**19**) was prepared from the appropriate 6-nitrile in boiling aqueous NaOH (87MIP4). Esters were obtained from 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids [85GEP3525108; 89JAP(K)89/165589]. Prodrugs were prepared from **19** with chloromethyl alkanoates in MeCN in the presence of K<sub>2</sub>CO<sub>3</sub> (92AF70). Ofloxacin was esterified by a 3-hydroxymethyl carbapenem derivative (91EUP451764), by dexamethasone and triamcinolone acetone (95EUP659763), and by *N*-hydroxysuccinimide (95PHA563). Heating 10-(1-*tert*-butoxycarbonyl-3-pyrrolidinyl)-9-fluoro-3-methyl-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate in a mixture of conc. HCl and AcOH gave 10-(3-pyrrolidinyl)-6-carboxylic acid derivative (90EUP390215).

The carboxyl group of 10-substituted 9-fluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids was converted into a (dialkoxycarbonyl)acetyl group by treatment with sodio malonate in  $\text{CHCl}_3$  in the presence of carbonyldiimidazole (94MIP4). 6-Carboxylic acids undergo ready decarboxylation in the presence of cyanide ion (94TL8303). Amidation of [(5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-7-yl)methylthio]acetic acid with amines afforded the corresponding *N*-substituted acetamide [96JAP(K)96/59620].

2,3-Dihydro-7-hydroxy-5-oxo-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxamides were prepared from the 6-esters with amines, from 6-carboxylic acids with amines in the presence of 1,3-dicyclohexylcarbodiimide, or by treatment with amines and  $\text{PCl}_3$  (93MIP4). 6-Carboxylic acids were obtained from the 6-esters by hydrolysis in a mixture of  $\text{HBr}$  and  $\text{AcOH}$ . Catalytic reduction of the 9-nitro group in 5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-ones over  $\text{PtO}_2$  in THF gave 9-amino derivatives. The nitro group of 9-fluoro-8-nitro-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one was reduced to an amino group by treatment with  $\text{Zn}$  dust in aqueous  $\text{EtOH}$  in the presence of  $\text{NH}_4\text{Cl}$  (89EUP406993). The 8-amino group in the 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one skeleton reacted with 3,4,5,6-tetrahydrophthalic anhydride in  $\text{AcOH}$  (89EUP406993). The 7-hydroxy-9-nitro derivative was *O*-acylated with  $\text{Ac}_2\text{O}$  in pyridine, and after reduction the 7-acetoxy-9-amino derivative was treated with  $\text{K}_2\text{CO}_3$  in DMF at room temperature to give the 7-hydroxy-9-acetylamino derivative. Depending on the molar ratio, oxidation of 6-[*N*-methyl-*N*-(4-methylthiophenyl)carbamoyl]-2,3-dihydro-7-hydroxy-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-one with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave sulfoxide and sulfone. A side-chain ethoxycarbonyl group in the 6-(1-indoliny)lcarbonyl moiety of 5-oxo-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine was hydrolyzed to a carboxylic group.

7-Benzoyloxy-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazine-3,8-dione was converted into the 7-hydroxy derivative in conc.  $\text{HCl}$  (83AJC2307). The 3-hydroxymethyl group was acylated with 3,5-dinitrobenzoyl chloride in the presence of pyridine, and the 3-[(3,5-dinitrobenzoyl)oxy]methyl group of ethyl 3-[(3,5-dinitrobenzoyloxy)methyl]-9,10-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate was selectively hydrolyzed with ethanolic aqueous  $\text{NaHCO}_3$  at  $50^\circ\text{C}$  to give the 3-hydroxymethyl ester (86AAC163, 86EUP206283; 87CPB1896). The 3-hydroxymethyl derivative was also obtained from 3-methoxymethyl and 3-(2-tetrahydropyranyloxymethyl) derivatives of 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate by treatment with  $\text{AlBr}_3$  in the presence of  $\text{EtSH}$  in  $\text{CH}_2\text{Cl}_2$  (84EUP101829), and the carboxylate by treatment with *p*-TSA (89GEP3913245), respectively. Acidic hydrolysis of 7-formamido-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-

one gave the 7-amino derivative, which was converted into the 7-dimethylamino derivative by treatment with a mixture of  $\text{CH}_2\text{O}$  and  $\text{HCO}_2\text{H}$  [69CR(C)564]. A side-chain 3,7-diazabicyclo[3.3.0]oct-1(5)-en-3-yl group in the 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine skeleton was N-methylated at position 7 with a mixture of 36% aqueous  $\text{CH}_2\text{O}$  and  $\text{HCO}_2\text{H}$  (91EUP424851).

The hydroxy and amino groups of 3-(3-hydroxy or 3-aminophenyl)perhydropyrido[2,1-*c*][1,4]oxazines were acetylated with  $\text{Ac}_2\text{O}$  (78JMC460). The hydroxy group of 6-hydroxy-3,10-dimethyl-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine reacted with  $\text{ClSO}_3\text{H}$  in abs. DMF (88GEP3817565; 90GEP3940081). The amino group of 1-aminoperhydropyrido[2,1-*c*][1,4]oxazines was acylated with (het)aroyl chlorides (92EUP514267). The amino groups of 8- and 9-aminoperhydropyrido[2,1-*c*][1,4]oxazines were acylated with 4-acetamido-5-chloro-2-methoxybenzoyl chloride in the presence of  $\text{NEt}_3$  in toluene (81EUP34015; 82EUP57536; 92BMC523, 92BMC1293), and the acetamido groups were hydrolyzed to an amino group by refluxing in aqueous EtOH in the presence of KOH. The amino group of *trans*-3,9*a*-*H*-3-aminomethylperhydropyrido[2,1-*c*][1,4]oxazine was acylated with 4-amino-5-chloro-2-methoxybenzoic acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide HCl in  $\text{CH}_2\text{Cl}_2$  (92CPB652).

The hydroxy group of 7-hydroxy-1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline was acylated with tosyl chloride, and the tosyloxy group was eliminated by the treatment with *tert*-BuOK to give 1,3,4,11*b*-tetrahydro-[1,4]oxazino[3,4-*a*]isoquinoline (67BRP1094470, 67NEP 6611733).

The formyloxy group of *cis*-8,9*a*-*H*-8-formyloxiperhydropyrido[2,1-*c*][1,4]oxazin-4-ones were hydrolyzed to a hydroxy group under basic conditions (81EUP34015; 85T2007). The 8-hydroxy group was oxidized to an oxo group with 9-fluorenone in the presence of *tert*-BuOK in benzene at room temperature (81EUP34015).

The mercapto group of 3-mercapto-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]-oxazin-4-ones reacted with *p*-nitrobenzyl (5*S*,6*S*)-2-(diphenylphosphono)oxy-6-[1(*R*)-hydroxyethyl]carbapen-2-em-3-carboxylates in the presence of *N,N*-diisopropylethylamine (86EUP168707, 86EUP169410). 3,4-Dihydro-1*H*,8*H*-pyrido[2,1-*c*][1,4]oxazine-8-thione was alkylated with diphenylmethyl 3-iodomethyl-7-acylamino-3-cephem-4-carboxylates [89JAP(K) 89/290683].

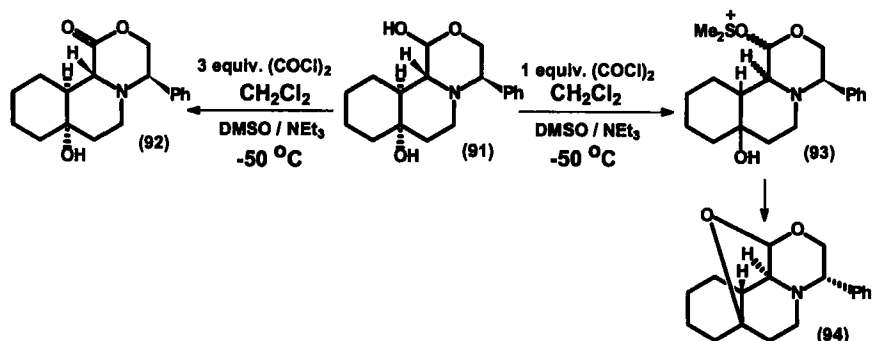
8,9-Methylenedioxy-1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinolin-1-one was obtained from the 8,9-dihydroxy derivative with  $\text{CH}_2\text{Br}_2$  (85MI12).

Catalytic reduction of 8,9-dinitro-2,5,6,7-tetrahydro-3*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-ones over Pt catalyst gave 8,9-diamino derivatives



[92PIA(A)549]. 8,9-Diamino groups were condensed with benzil [92PIA(A)549]. Ozonolysis of 2-benzylidene-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one afforded the 2,3-dioxo derivative [92PIA(A)549]. Catalytic reduction of 9-nitro-2,5,6,7-tetrahydro-3*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one over Raney Ni gave the 9-amino derivative, and the amino group was converted to a bromo atom via the diazonium salt with  $\text{Cu}_2\text{Br}_2$  (84GEP3234529). Catalytic reduction of 8-nitro-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid over 5% Pd-C in DMF gave an 8-amino derivative (91JMC1142). A 1-nitrocyclopropyl group in the 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate skeleton was reduced to an 1-aminocyclopropyl group [96JAP(K)96/41070]. A 1-oxo-1,5,6,11-tetrahydroimidazo[4,5-*g*]pyrido[1,2,3-*de*][1,4]benzoxazine-2-carboxylic acid derivative was obtained when a 9-amino-8-nitro-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was hydrogenated over Pd-C and the 8,9-diamino derivative was reacted with  $\text{HC}(\text{OEt})_3$  (96CPB987).

The hydroxy group of 1-hydroxy-4-phenyl-8-substituted perhydropyrido[2,1-*c*][1,4]oxazines was oxidized to the oxo group by the Swern method (90SL731; 92T431), and it was silylated with  $\text{Me}_3\text{SiCl}$  (92T431). The silyloxy derivatives were desilylated by treatment with  $\text{Bu}_4\text{NF}$ . Swern oxidation of 1,7*a*-dihydroxyperhydro[1,4]oxazino[4,3-*b*]isoquinoline (**91**) gave the 1-oxo derivative **92** when an excess (3 eq) of oxidizing reagents was used. Otherwise, **94** was produced, presumably via intramolecular nucleophilic substitution of the oxosulfonium moiety of **93** by the tertiary hydroxy group (92T431).



The azido group of 10-azido-9-fluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate was catalytically reduced to an amino group over Pd (89EUP306860), and the amino group was changed to a

bromo atom by treatment with  $\text{Cu(II)Br}_2$  and  $n\text{-BuNO}_2$  (89EUP306860; 94USP5308843). (*S*)-10-(1-Aminocyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was prepared from the 10-cyano(ethoxycarbonyl)methyl derivative on heating in dioxane in the presence of *p*-TSA, followed by treatment of the 10-cyanomethyl derivative with  $\text{BrCH}_2\text{CH}_2\text{Br}$  in aqueous NaOH in the presence of  $\text{Et}_3\text{Ph}(\text{CH}_2)\text{NBr}$  at  $45^\circ\text{C}$ . The cyano group was then hydrolyzed to an aminocarbonyl group in conc.  $\text{H}_2\text{SO}_4$  and was converted into an amino group by a Hofmann rearrangement in the presence of NaOCl [96JAP(K)96/41070].

The oxo groups of 8- and 9-oxoperhydropyrido[2,1-*c*][1,4]oxazines were converted to amino groups by condensation with  $\text{HONH}_2 \cdot \text{HCl}$  in pyridine, followed by reduction with LAH, or with Na in amyl alcohol (81EUP34015; 82EUP57536; 92BMC1293). *trans*-8,9*a*-H-8-Aminoperhydropyrido[2,1-*c*]-[1,4]oxazines were prepared from *cis*-8,9*a*-H-8-hydroxy derivatives and from its 4-oxo derivatives via *trans*-8,9*a*-H-8-azido derivatives by treatment with  $\text{Ph}_3\text{P-DEAD-(PhO)}_2\text{PON}_3$ , then with LAH (81EUP34015; 92BMC523). The hydroxy group of *cis*-8,9*a*-H-8-hydroxyperhydropyrido[2,1-*c*][1,4]oxazin-4-one was silylated with bis(trimethylsilyl)amine (92BMC523) and hexamethyldisilazane (81EUP34015). The oxo group of *cis*-8,9*a*-H-8-trimethylsilyloxyperhydropyrido[2,1-*c*][1,4]oxazin-4-one was converted to a Me and a Ph group by treatment with  $\text{MeMgBr}$  and  $\text{MeLi}$  or  $\text{PhLi}$  and then with  $\text{NaBH}_4$  (81EUP34015; 92BMC523). 2,5,6,7-Tetrahydro-3*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-thione was prepared from its 3-oxo derivative with  $\text{P}_4\text{S}_{10}$  in  $\text{PhCl}$  (84GEP3234529). 1,3,4,6,7,11*b*-Hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamides were prepared from esters with  $\text{NH}_4\text{OH}$  and amines (68SAP68/02790; 70MIP1), and from 3-carboxylic acids via acid chlorides, mixed anhydrides, and active esters with amines (68SAP68/02790; 78JMC785). The 3-nitrile was obtained from the 3-carboxamide with  $\text{POCl}_3$ , and the nitrile was hydrolyzed to the 3-carboxylic acid in boiling 2 N NaOH, converted into its 3-ester by the treatment in MeOH with HCl, or in EtOH with KOH, and to 3-carboxamide in boiling *tert*-BuOH with *tert*-BuOK (68SAP68/02790; 78JMC785).

Reaction of 9-fluoro-8-isothiocyanato- and 8-iso(thio)cyanato-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines with 2-amino-4,4-dimethylpyrrolidine, then with  $\text{Br}_2$ , and with ethyl pipercolinate yielded 8-(6,6-dimethyl-3,5,7,7-tetrahydropyrrolo[2,1-*c*][1,2,4]thiadiazol-3-ylidenamino)-9-fluoro and 8-(1,3-dioxo and 1-oxo-3-thioxoperhydroimidazo[1,5-*a*]-pyridin-2-yl) derivatives, respectively (89EUP406993). Treatment of 9-fluoro-8-(2-hydroxymethylpiperidinothiocarbonylamino)-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine with HCl gas in EtOH gave the 8-(perhydropyrrolo[1,2-*c*]thiazol-3-ylidenamino) derivative.

Boron chelates, e.g., **90**, were obtained from carboxylic acids **89** or esters with  $\text{BF}_3$  etherate (86EUP206283; 87ABC1265, 87CPB1896; 88EUP273399; 90EUP368410) and with  $\text{HBF}_4$  [84JAP(K)84/67290], or from their ethyl ester by heating in an anhydride in the presence of  $\text{H}_3\text{BO}_3$  [85JAP(K)85/75489, 85JAP(K)85/78986; 87CPB1896].

The acetyl group of 10-acetyl-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was brominated with  $\text{KBrO}_3$  and 48%  $\text{HBr}$  acid in  $\text{AcOH}$ , and the 2-bromoacetyl group was then converted into a 10-[2-aminomethyl-4-thiazolyl] group with phenylmethyl (2-amino-2-thioxoethyl)carbamate and subsequent treatment with 32%  $\text{HBr}$  (87JHC1509).

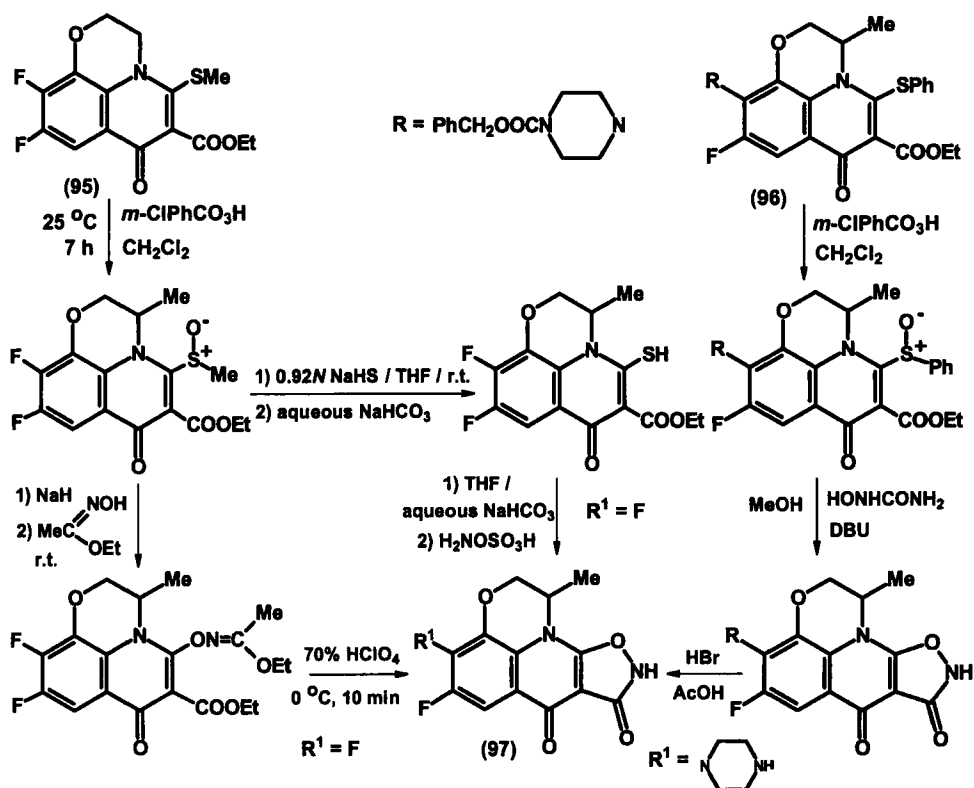
Side-chain halogen atoms in [1,4]oxazino[4,3-*b*]isoquinolines and pyrido[1,2,3-*de*]-1,4-benzoxazine-3-one were reduced with tri-*n*-butyltin hydride in benzene at  $90^\circ\text{C}$  (79T2345) or catalytically over  $\text{Pd}$  [70CR(C)498], respectively. Side-chain *tert*-butoxycarbamoyl, trifluoroacetamido, and acetamido groups in pyrido[1,2,3-*de*]-1,4-benzoxazines were hydrolyzed into an amino group under basic or acidic conditions (84EUP101829; 86EUP172651; 87EUP208210; 88EUP265230, 88JMC983; 89EUP324298; 90EUP388298, 90MIP2; 91EUP413455; 92EUP488227, 92USP5097032, 92USP5164402; 94CPB1442, 94CPB2629, 94GEP4230804). A benzyloxycarbonylamino group was converted into an amino group by hydrogenation over  $\text{Pd-C}$  [90JAP(K)90/264724; 94CPB2063, 94CPB2569], or by treatment with  $\text{CF}_3\text{COOH}$  (95MIP4). A side-chain 2-*tert*-butoxycarbonylcyclopropyl group in pyrido[1,2,3-*de*]-1,4-benzoxazine was converted to a 2-carboxylcyclopropyl group by treatment with  $\text{CF}_3\text{COOH}$  (89GEP3913245). The 2-carboxyl group reacted with ethyl chloroformate in the presence of  $\text{NEt}_3$ , then with  $\text{NaN}_3$ , and finally with benzyl alcohol to give a 2-benzyloxycarbonylamino group (89GEP3913245).

A benzyloxycarbonylamino group in a side-chain cyclopropyl group in the 2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-7-one skeleton was converted into an amino group by treatment with 30%  $\text{HBr}$  and by hydrogenation over 5%  $\text{Pd-C}$ , respectively. Acetamido and dimethylamino groups were obtained from the amino group with  $\text{Ac}_2\text{O}$  and with 37% formaldehyde and  $\text{NaBH}_3\text{CN}$ , respectively. An acetamido group was methylated with  $\text{MeI}$  in the presence of  $\text{NaH}$ , and hydrolyzed on heating in 6 *N*  $\text{HCl}$  to a methylamino group (89GEP3913245).

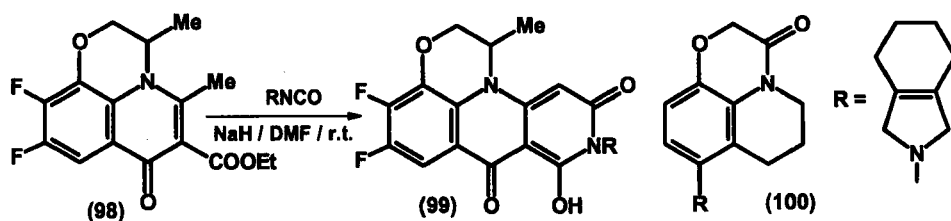
The hydroxy group of 6-hydroxy-2,3,5,6-tetrahydroxy-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine reacted with  $\text{ClSO}_3\text{H}$  at  $0^\circ\text{C}$  in  $\text{CCl}_4$  (48USP2448869). The side-chain hydroxy group of 3-hydroxymethyl-9,10-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2, 3-*de*]-1,4-benzoxazine-6-carboxylate was acylated with 3,5-dinitrobenzoyl chloride (87CPB1896), and  $\text{MeCO}_2\text{Cl}$  (89GEP3913245; 94CPB2569). It was converted to a fluorine atom with

$\text{Et}_2\text{NSF}_3$  in dry  $\text{CH}_2\text{Cl}_2$  [86JAP(K)86/271292; 87CPB1896], to a chlorine atom with  $\text{SOCl}_2$  (84EUP101829), and to an iodine atom with triphenylphosphite methiodide in DMF, and it was reduced with tri-*n*-butyltin hydride in EtOH to give the methyl derivative (86AAC163, 86EUP206283; 87CPB1896). 3-Methylene derivatives were prepared from 3-chloromethyl (84EUP101829), and 3-mesyloxymethyl compounds (89GEP3913245; 94CPB2569) by elimination of  $\text{HCl}$ , or  $\text{MeSO}_3\text{H}$  with dizabicyclo[5.4.0]undec-7-ene (DBU).

Tetracyclic derivatives **97** were prepared from 5-methylthio and 5-phenylthio derivatives of 7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates **95** and **96**, according to Scheme 7 (87EUP228661). Reaction of 5-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate **98** with isocyanates afforded derivatives of tetracyclic ring system **99** [92JAP(K)92/91090].



SCHEME 7

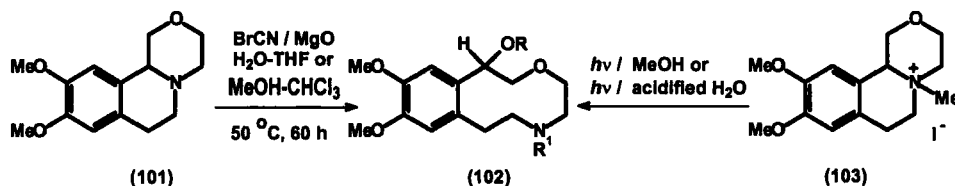


Reaction of 8-amino-2,5,6,7-tetrahydro-3*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one with tetrahydropthalic anhydride gave **100** (91EUP406993). The hydroxy group of 9-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-2,3-dihydro-5*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazin-5-ones was acylated (79GEP2854727). Treatment of 9-fluoro-10-phenyl-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate with  $\text{ClSO}_3\text{H}$  afforded the 10-(*p*-chlorosulphonylphenyl) derivative, which was converted to the 10-(*p*-aminosulphonylphenyl) derivative with  $\text{NH}_3$  (86EUP184384).

The piperaziny group of 9-fluoro-3-methyl-10-(1-piperazinyl)-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid was *N*-alkylated with *n*-BuBr in aqueous DMF in the presence of  $\text{Na}_2\text{CO}_3$  (90EUP354453). Photodegradation of **19** (94JPS463) and **20** (93AF601), which occurred in the 10-(4-methylpiperazin-1-yl) moiety, was investigated in aqueous solution, (93AF601). Photodegradation of pazufloxacin was investigated in aqueous solution and in the solid state (95YZ716).

### 5. Ring Transformations

Treatment of 3-phenyl-1-oxo-1*H*-pyrido[2,1-*c*][1,4]oxazinium bromide with  $\text{NH}_4\text{OAc}$  in AcOH, then with  $\text{Ac}_2\text{O}$  yielded 1-hydroxy-3-phenylpyrido[1,2-*a*]pyrazinium bromide (64CB3566). 6,10-Dioxo-6,10-dihydropyrido[2,1-*c*][1,4]benzoxazine-7,8-dicarboxylate was rearranged into 1-(2-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-4,5-dicarboxylate by heating in DMF [85H(23)2401; 89JHC847].



Treatment of 1,3,4,5,6,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline **101** with BrCN in the presence of MgO gave the 1-hydroxy or 1-methoxy derivative of 3,6-benzoxazine **102** ( $\text{R}^1 = \text{CN}$ ,  $\text{R} = \text{H}$  or  $\text{Me}$ ) [79CI(L)319; 86AJC893]. 3,6-Benzoxazine **102** ( $\text{R} = \text{R}^1 = \text{Me}$ ) was also obtained by

photosolvolytic cleavage of the quaternary iodide **103** [80CI(L)421; 85AJC1591].

## 6. Miscellaneous

Enantiomers of 3-[(3,5-dinitrobenzoyloxy)methyl-9,10-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate were separated by preparative HPLC (86AAC163, 86EUP206283; 87CPB1896). Resolution of racemic *N,N*-diethyl-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-3-carboxamide was carried out by using enantiomers of malic acid in 2-propanol (68SAP68/02790; 78JMC785). Ofloxacin (**19**) was resolved into its enantiomers by amination with H<sub>2</sub>NSO<sub>2</sub>OH, followed by treatment with (*S*)-(+)-mandelic acid, then by reductive deamination (88GEP3639465). Methyl esters **19** were resolved into the enantiomers by a liquid chromatographic column containing 22 wt. % cellulose tris(dimethylphenylcarbamate) deposited on silica gel [89JAP (K)89/305091]. The photostability of ofloxacin (**19**) was investigated in aqueous NaOH solution with long-wavelength UV light (92AAC1715).

## B. PYRIDO[1,2-*a*][1,4]THIAZINES AND THEIR BENZO DERIVATIVES

### 1. Ring Opening

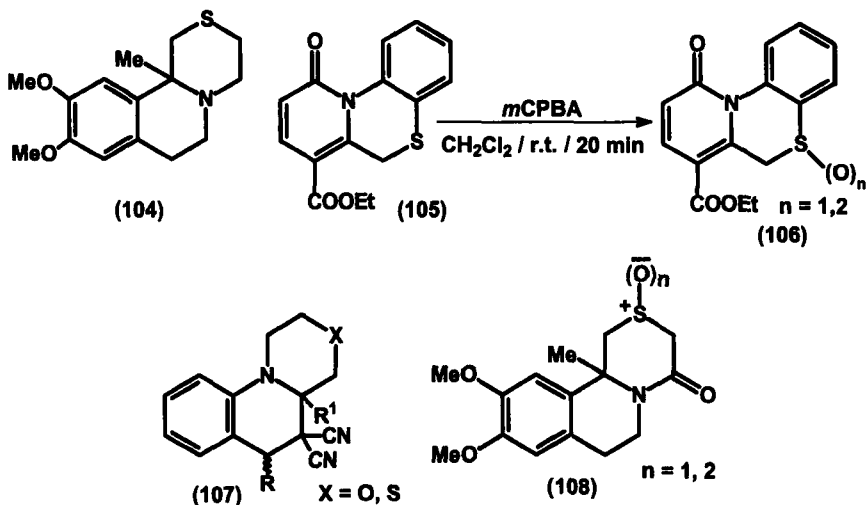
Treatment of 1,2-dihydro[1,4]thiazino[4,3-*a*]quinolin-1-ones with NaBH<sub>4</sub> in EtOH afforded 2-[(2-hydroxyethyl)thiomethyl]quinolines (73IJC1051). Desulfurization of 8-formyloxy-8-methylperhydropyrido[2,1-*c*][1,4]thiazin-4-one with Raney Ni in boiling EtOH gave 1-acetyl-2,4-dimethyl-4-piperidinol (82TL3811; 85T2861).

### 2. Reduction

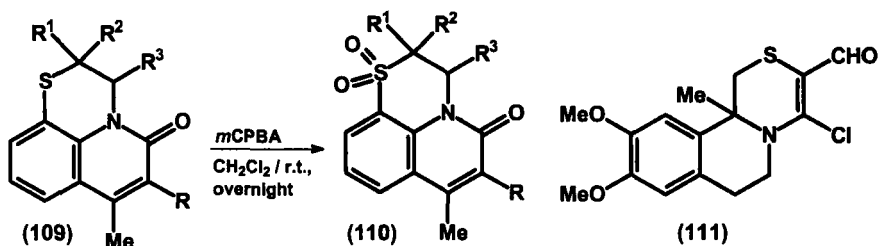
Reduction of *cis*-8,9*a*-H-8-formyloxyperhydropyrido[2,1-*c*][1,4]thiazin-4-one with LAH gave *cis*-8,9*a*-H-8-hydroxyperhydropyrido[2,1-*c*][1,4]thiazine (81EUP34015). 11*b*-Methyl-1,3,4,6,7,11*b*-hexahydro[1,4]thiazino[3,4-*a*]isoquinoline **104** was obtained from 4-oxo derivative **45** by treatment with BH<sub>3</sub> in THF (80JHC449; 81CP1101857).

### 3. Reactivity of Ring Hetero Atoms

Methiodides have been prepared from perhydropyrido[2,1-*c*][1,4]thiazines [57N559; 59AP(292)165].



Oxidation of perhydropyrido[2,1-*c*][1,4]thiazine with both 30%  $\text{H}_2\text{O}_2$  in boiling AcOH and monoperoxyphthalic acid in  $\text{Et}_2\text{O}$  at  $-120^\circ\text{C}$  yielded the 2,2-dioxide [57N559; 59AP(292)165]. Oxidation of either epimer of 8- and 9-(*N*-aroylamido)perhydropyrido[2,1-*c*][1,4]thiazines with  $\text{NaIO}_4$  gave sulfoxides (81EUP34015; 82EUP57536; 92BMC1293). Oxidation of pyrido[2,1-*c*][1,4]benzothiazine **105** with *m*-CPBA gave a mixture of the 6-oxide **106** ( $n = 1$ ) and the 6,6-dioxide **106** ( $n = 2$ ) (90FES589). A mixture of epimers of sulfoxide and sulfone were obtained from **107** ( $X = \text{S}, R = R^1 = \text{H}$ ) by oxidation with 1 or 2 eq *m*-CPBA, respectively (95TL5159). Oxidation of 1,3,4,6,7,11*b*-hexahydro[1,4]thiazino[3,4-*a*]isoquinolin-4-one **45** with *m*-CPBA and with  $\text{NaIO}_4$  afforded the 2,2-dioxide **108** ( $n = 2$ ) and an epimeric mixture of the 2-oxide **108** ( $n = 1$ ), respectively (80JHC449; 81CP1101857). Hexahydro[1,4]thiazino[3,4-*a*]isoquinoline **104** was oxidized to an epimeric mixture of 2-oxides with  $\text{NaIO}_4$  (80JHC449). Oxidation of 5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazin-5-ones and their 2,3-dihydro derivative (**109**) with *m*-CPBA yielded sulfoxides (93MIP4) and sulfones **110** (81JHC1273; 82JHC237; 93MIP4) depending on the molar ratios. Sulfoxides were prepared from 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids and esters with  $\text{Pb}(\text{OAc})_4$  in AcOH in the presence of KBr at  $30^\circ\text{C}$  (87JMC465), with *m*CPBA in EtOH at room temperature (88EUP267432; 93JMC3449), with a mixture of potassium monopersulfate,  $\text{KHSO}_4$ , and  $\text{K}_2\text{SO}_4$  in aqueous propionic acid (93BMC1711; 94USP5308843), and with 1 mol eq of 30%  $\text{H}_2\text{O}_2$  in AcOH at  $100^\circ\text{C}$  (88EUP252352; 90EUP368410) or in formic acid at  $40^\circ\text{C}$  (89EUP310969). When more than 2 moles of 30%  $\text{H}_2\text{O}_2$  were applied, 1,1-dioxides were obtained (87JMC465).



1-Oxides of 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids and esters could be reduced with  $\text{PCl}_3$  or  $\text{PBr}_3$  in DMF to give 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids and esters (87JMC465; 88EUP252352; 88EUP267432; 89EUP310969; 90EUP368410; 93JMC3449).

#### 4. Reactivity of Ring Carbon Atoms

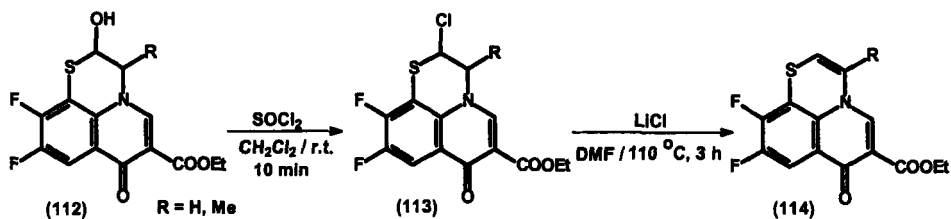
7-Benzyl-6-oxoperhydropyrido[2,1-*c*][1,4]oxazine-4-carboxylic acid was prepared from the 7-unsubstituted derivative by alkylation with  $\text{PhCH}_2\text{Br}$  in the presence of lithium bis(trimethylsilyl)amide in THF at  $-78^\circ\text{C}$  (96MIP8). The reaction of 1,3,4,6,7,11*b*-hexahydro[1,4]thiazino[3,4-*a*]-isoquinolin-4-one (**45**) with a Vielsmeier-Haack reagent afforded 3-formyl-4-chloro-1,6,7,11*b*-tetrahydro[1,4]thiazino[3,4-*a*]isoquinoline (**111**) (81CP 1101857).

Although no decyanation occurred from 5,5-dicyano-1,2,5,6-tetrahydro-4*H*-[1,4]thiazino[4,3-*a*]quinoline (**107**,  $\text{X} = \text{S}$ ,  $\text{R} = \text{R}^1 = \text{H}$ ) and its sulfoxides with a mixture of  $\text{Bu}_3\text{SnH}$  and 2,2'-azobisisobutyronitrile, the reductive radical decyanation of its sulfone afforded the 3,3-dioxide derivative of 5-cyano-1,2,5,6-tetrahydro-4*H*-[1,4]thiazino[4,3-*a*]quinolines as a 9 : 1 mixture (95TL5159).

Depending upon the molar ratio, either the 6-bromo or the 6,6-dibromo derivative was obtained from 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-3,7-dione with  $\text{Br}_2$  in AcOH (72AJC1283). Treatment of 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-3,7-dione with  $\text{H}_2\text{O}_2$  in AcOH, or with *t*-butyl hypochlorite in  $\text{CHCl}_3$ -EtOH gave the 2-acetoxy and 2-ethoxy derivatives, respectively. The reactions may proceed via a sulfoxide and subsequent Pummerer rearrangement to give the final products (72AJC1283). 7-Oxime was prepared from a 3,7-dione derivative [80JAP(K)80/111406]. Reduction of 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-3,7-dione with  $\text{NaBH}_4$  afforded the 7-hydroxy-3-oxo derivative [72AJC1283; 80JAP(K)80/111406].

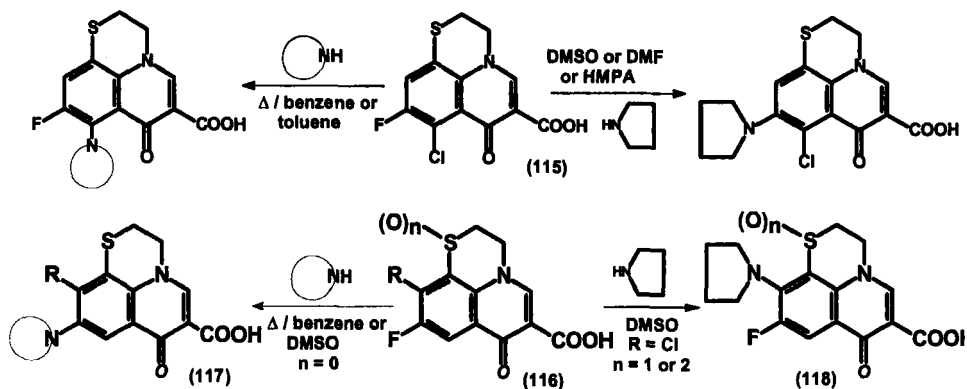
No dehydration of 2-hydroxy-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates (**112**) occurred on treatment with conc.





$\text{H}_2\text{SO}_4$  or tosyl chloride in pyridine (91JHC1067). The latter reaction did not even afford the corresponding tosylate. The chlorides **113** were prepared from hydroxides **112** with  $\text{SOCl}_2$ . The base-catalyzed E2-type dehydrochlorination of **113** using pyridine or DBU as the base failed to give compounds **114**. However, when the *cis*-elimination method using LiCl was applied, the desired 7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates (**114**) were obtained in good yields.

The regioselectivity of the nucleophilic substitution of the halogen atoms of 8-chloro-9-fluoro-7-oxo-pyrido[1,2,3-*de*][1,4]benzothiazine-6-carboxylic acid (**115**) with cyclic amines depends on the nature of the solvent (Scheme 8), but 10-chloro-9-fluoro-7-oxo-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid (**116**,  $n = 0$ ,  $R = \text{Cl}$ ) afforded only 9-substituted derivatives **117** ( $R = \text{Cl}$ ), independent of the reaction conditions (87JMC465). However, when its 1-oxide or 1,1-dioxide derivatives **116** ( $n = 1, 2$ ;  $R = \text{Cl}$ ) were involved in the reactions, 10-substituted derivatives **118** were regioselectively obtained (87JMC465; 88EUP252352, 88EUP267432; 89EUP310969; 90EUP368410; 93JMC3449). The 9-fluoro derivative **116** ( $n = 0$ ,  $R = \text{H}$ ) also reacted with cyclic amines, but the reaction of 9,10-dichloro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid with cyclic amines under different conditions (solvent, elevated temperature,



Scheme 8

autoclaved reaction) failed (87JMC465). Earlier it was claimed that 9,10-dichloro derivatives reacted with cyclic amines at 180°C [84 JAP(K)84/76091]. Regioselective substitution of the 10-fluoro atom of 9,10-difluoro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids and their 2,3-dihydro derivatives with cyclic amines proceeded smoothly to give the 9-fluoro-10-substituted derivatives [82JAP(K)82/203085; 90 EUP368410; 91JHC1061, 91JHC1067; 94JMC4195, 94MIP1].

### 5. Reactivity of Substituents Attached to Ring Carbon Atoms

The formyloxy group of *cis*-8,9*a*-*H*-8-formyloxyperhydropyrido[2,1-*c*][1,4]-thiazin-4-one was hydrolyzed to a hydroxy group and the hydroxy group was oxidized to an oxo group with fluorenone in the presence of *tert*-BuOK in benzene at ambient temperature (81EUP34015). 6-Oxoperhydropyrido[2,1-*c*][1,4]oxazine-4-carboxylic acid was obtained by hydrolysis of the ethyl ester in the presence of LiOH in aqueous THF at 0°C (96MIP8). An amide was prepared from 4-carboxylic acid.

Perhydropyrido[2,1-*c*][1,4]-thiazine-4,4-diphosphoric acid was prepared from its 4-one derivative by treatment with H<sub>3</sub>PO<sub>4</sub>, then PCl<sub>3</sub> at 100°C, followed by addition of H<sub>2</sub>O (88GEP3719513).

The condensation of octahydropyrido[2,1-*c*][1,4]thiazin-8-one and -9-one with HONH<sub>2</sub> HCl in pyridine and subsequent reduction with LAH gave an epimeric mixture of 8-amino- and 9-aminoperhydropyrido[2,1-*c*][1,4]thiazines (81EUP34015; 82EUP57536; 92BMC1293). The 8-hydroxy derivative was converted into an epimeric mixture of 8-aminoperhydropyrido[2,1-*c*][1,4]thiazine via the 8-azido derivatives by treatment with Ph<sub>3</sub>P-DEAD-(PhO)<sub>2</sub>PON<sub>3</sub>, then with LAH (81EUP34015). The amino groups of an epimeric mixture of 8-amino- and 9-aminoperhydropyrido[2,1-*c*][1,4]thiazines were acylated with 4-acetamido-5-chloro-2-methoxybenzoyl chloride and other aroyl chlorides, and the acetamido moieties were hydrolyzed to amino groups by treatment with NaOH (81EUP34015; 82EUP57536; 92BMC1293). The epimers were separated by column chromatography on silica.

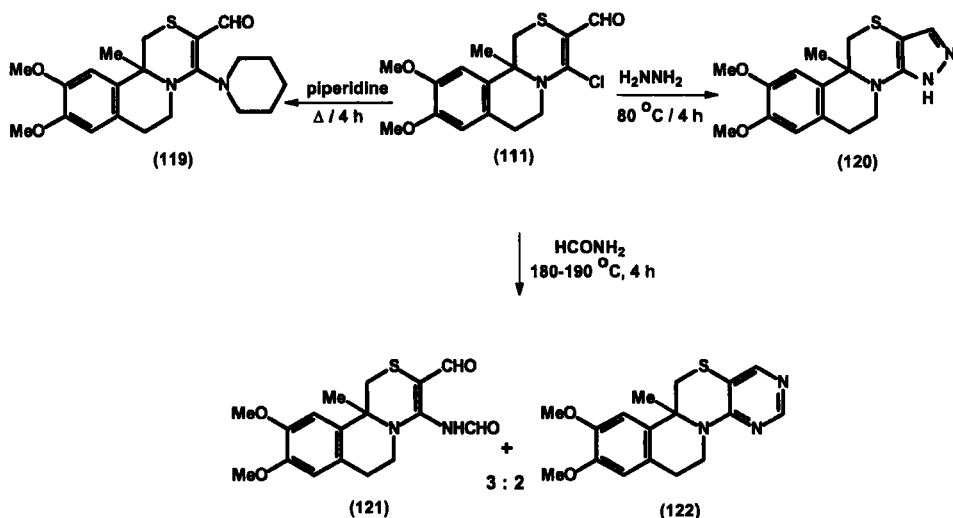
The piperazine moiety of 9-(1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate was *N*-acylated with trifluoroacetic anhydride under reflux for 2 h (87JMC465).

Ethyl, methyl 10-oxo-6,10-dihydropyrido[2,1-*c*][1,4]benzothiazine-7,8-dicarboxylate was hydrolyzed by heating with 0.5 N NaOH in ethanol at 60°C to give the corresponding 7,8-dicarboxylic acid, which was decarboxylated by heating in Dowtherm A at 230°C to yield 10-oxo-6,10-dihydropyrido[2,1-*c*][1,4]benzothiazine-8-carboxylic acid (86USP4576942). Treatment of diethyl 10-oxo-6,10-dihydropyrido[2,1-*c*][1,4]benzothiazine-

7,9-dicarboxylate with aqueous  $\text{NH}_3$  in boiling ethanol for 5 h gave the 9-carboxamido and 7,9-dicarboxamido derivatives, depending on the reaction time (90FES589). Similarly, 10-oxo-6,10-dihydropyrido[2,1-*c*][1,4]benzothiazine-7-carboxamide was prepared from the appropriate ethyl ester.

The reactions of **111** with piperidine, hydrazine hydrate and formamide gave the 3-amino derivatives **119** and **121** and the tetracyclic products **120** and **122** (81CP1101857). The 9,10-dihydroxy derivative was prepared from **45** on treatment with  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  for 3 h (80JHC449; 81CP1101857).

Bis derivatives **44** ( $n = 0, 1$ ) were prepared from 2-mercapto-2-methyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium chloride in EtOH in the presence of pyridine by air oxygen, and in MeOH by  $\text{SeO}_2$  at  $-5^\circ\text{C}$ , respectively (95SUL281).



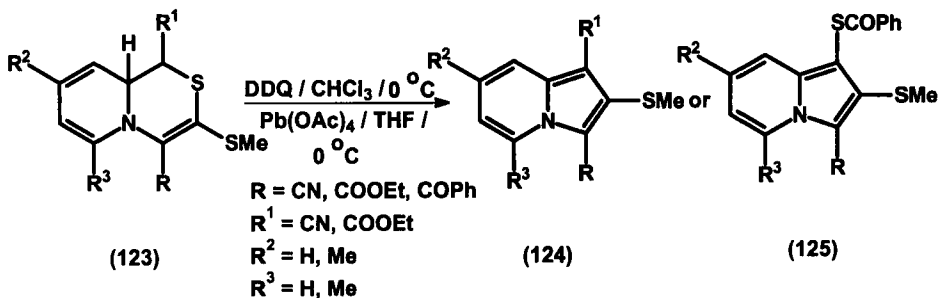
The ester and nitrile (87MIP4) groups of different 7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates and -6-carbonitrile were hydrolyzed under acidic (87USP4636506; 88EUP252352; 89EUP306860, 89EUP310969; 90EUP368410; 91JHC1061, 91JHC1067; 93BMC1711, 93MIP4; 94CPB2569; 95MIP1, 95MIP2) or basic conditions [85JAP(K) 85/208987; 87JMC465, 87MIP4, 87USP4636506; 88EUP267432; 89GEP3913245; 90EUP376870; 91SC2301; 93EUP522277, 93JMC3449]. Carboxamides were prepared from 7-hydroxy-2,3-dihydro-5-oxo-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids via acid chlorides, and from esters with secondary amines (93MIP4). The hydroxyl group of 9-(1-

hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazin-5-ones was alkylated and acylated (79GEP2854725). Amidation of [(5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzthiazin-7-yl)methylthio]acetic acid with amines afforded the corresponding *N*-substituted acetamide [96JAP(K)96/59620].

The 10-(1-aminocyclopropyl) derivative was obtained from 10-(1-benzoyloxycarbonylamino-cyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid in AcOH under H<sub>2</sub> in the presence of 5% Pd-C (89GEP3913245), and by treatment with 30% HBr-AcOH at 5–10°C (94CPB2569). The benzoyloxymethyl group of ethyl 3-(benzoyloxymethyl)-10-chloro-9-fluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate was hydrolyzed by treatment with EtONa in EtOH, followed by H<sub>2</sub>O (89EUP310969). The hydroxymethyl group was converted to fluoromethyl group with Et<sub>2</sub>NSF<sub>3</sub> (89EUP310969).

## 6. Ring Transformations

Epimeric mixtures of 3-methylthio-4-cyano- and -4-ethoxycarbonyl-1,9*a*-dihydropyrido[2,1-*c*][1,4]thiazine-1-carboxylates (**123**; R = CN, COOEt; R<sup>1</sup> = COOEt; R<sup>2</sup> = R<sup>3</sup> = H) decomposed spontaneously at 0°C to afford aromatic indolizine-1-carboxylates (**124**; R = CN, COOEt; R<sup>1</sup> = COOEt; R<sup>2</sup> = R<sup>3</sup> = H) [85H(23)33]. Oxidation of 1,9*a*-dihydropyrido[2,1-*c*][1,4]thiazines (**123**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or with Pb(OAc)<sub>4</sub> gave indolizines **124** and **125** [87BCJ1867; 88JAP(K)88/238077].



## C. PYRIDO[1,2-*a*]PYRAZINES AND THEIR BENZO DERIVATIVES

### 1. Ring Opening

Heating 1-hydroxy-3-oxo-3,4-dihydropyrido[1,2-*a*]pyrazin-5-ium betaine in H<sub>2</sub>O afforded the ring-opened product [67JCS(C)2391]. Heating *cis*-

1-methoxy-9*a*-methyl-3-isopropyl-3,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]pyrazin-4-one and its 7,8-benzo derivative in HBr also yielded ring-opened products [87AG(E)143]. Cleavage of the N-5-C-6 and N-5-C-11*a* bonds occurred selectively on treatment of the methiodides of 1,2,3,4,11,11*a*-hexahydro-6*H*-pyrazino[1,2-*b*]isoquinolin-1-ones with Li in liquid NH<sub>3</sub> and by hydrogenation over PtO<sub>2</sub> under 100 atm at 100°C or on treatment with 5% sodium amalgam in 60% aqueous EtOH, respectively [73CPB2039; 74JAP(K)74/72274, 74JAP(K)74/72283]. Acidic hydrolysis of 11*b*-benzyl-2-methyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline-1,4-diones afforded 1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids [68JCS(CC)1450].

## 2. Hydrogenation, Reduction, Oxidation

Perhydropyrido[1,2-*a*]pyrazines were obtained by catalytic hydrogenation of pyrido[1,2-*a*]pyridazin-5-ium bromide and its substituted or partly saturated derivatives, and from pyrido[1,2-*a*]pyridazin-5-ium 2-oxide bromides over PtO<sub>2</sub> or Pd-C [66JOC941; 67JCS(C)2391; 71JCS(C)861; 76JA246; 94T1811]. Hydrogenation of 2-benzyl-7-[bis(*p*-fluorophenyl)methylene]perhydropyrido[1,2-*a*]pyrazin-6-one over Pd-C in AcOH afforded a *cis-trans* mixture of 7-[bis(*p*-fluorophenyl)methyl]perhydropyrido[1,2-*a*]pyrazin-6-one (93JOC690). 8-Hydroxyperhydropyrido[1,2-*c*]pyrazine was prepared both by the reduction of 8-hydroxy-3,4-dihydro-9*a*-*H*-pyrido[1,2-*c*]pyrazine with Na in MeOH and by catalytic hydrogenation of 2-acetylperhydropyrido[1,2-*c*]pyrazine-6,8-dione over Adams catalyst (64MI1). Catalytic hydrogenation of 3-aryl-2,6,7,8,9,9*a*-hexahydropyrido[1,2-*a*]pyrazin-1-ones over 10% Pd-C afforded perhydro derivatives (67NEP6613937). Perhydropyrido[1,2-*a*]pyrazin-1-one and perhydropyrido[1,2-*a*]pyrazin-3-one were obtained from both 1-oxo-1,2-dihydropyrido[1,2-*a*]pyrazin-5-ium bromide and its 3,4-dihydro derivative [67JCS(C)2391], and from 3-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazin-5-ium chloride (67YZ668) by hydrogenation over PtO<sub>2</sub>. Perhydropyrido[1,2-*a*]pyrazin-3-one was prepared from 3-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazin-5-ium chloride by hydrogenation over PtO<sub>2</sub> (67YZ668). Catalytic hydrogenation of 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*b*]isoquinolinium bromide and its 1-oxo-1,3,4,6-tetrahydro-2*H* derivative over PtO<sub>2</sub> gave 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (73CPB2039). Catalytic hydrogenation of 2-benzoyl-2,3,6,7-tetrahydro-4*H*-pyrazino-[2,1-*a*]isoquinolin-4-ones over PtO<sub>2</sub> and Raney Ni asymmetrically modified with (–)-tartaric acid yielded the (±)- and (–)-2-benzoyl-1,2,3,6,7,11*b*-hexahydro derivatives, respectively (75GEP2418111; 76GEP2441261). Catalytic hydrogenation of 2-acyl-1,2,3,11*b*-tetrahydro-4*H*- and 2-benzoyl-7-

methylene-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones over PtO<sub>2</sub> and 5% Pd-C gave 2-acyl (76GEP2441261, 76GEP2457971), and 2-benzoyl-7-methyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones (76GEP2441261). 2,3,4,4*a*,5,6-Hexahydro-1*H*-pyrazino[1,2-*a*]quinolin-2-one was prepared by catalytic hydrogenation of 2-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]quinolinium bromide over PtO<sub>2</sub> (63YZ679).

Reduction to a methylene group of the oxo group was achieved by LAH for all of the following: perhydropyrido[1,2-*a*]pyridazin-1-ones [60JOC2108; 66JMC311; 67JCS(C)2391, 67YZ668; 68USP3388128; 69JCS(C)1987, 69JHC181; 73CPB1248; 76KFZ(1)88; 94MIP7, 94USP 5354747; 95TA321, 95USP5461047], -3-ones [67YZ668; 68JOC2379; 72JCS(P2) 1374; 91JOC5192; 95JCS(P1)369], -4-ones [57N62; 59CB240; 72JCS(P2)1374], -6-ones (93JOC690) -1,3-diones (91T1065), and -1,4-dione **48** (R = R<sup>1</sup> = H) (93JMC2311; 94MIP2; 96MIP7); 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino-[1,2-*b*]isoquinolin-1-ones [64JOC326; 73CPB2039; 75IJC230; 77IJC(B)70] and -6-ones (73CPB2039); 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones (77GEP1795728; 85CB4620; 86MI4), -3-ones (71USP 3557120; 72USP3676444, 72USP3682926, 72USP3684813; 73USP3728352; 74USP3798223), -1,4-diones (71USP3557120; 72USP3676444, 72USP 3682926, 72USP3684813; 73USP3728352; 74USP3798223), and -3,4-dione (65BEP659249); and 2,3,4,4*a*,5,6-hexahydro-1*H*- and perhydropyrazino-[1,2-*a*]quinolin-4-ones (64JOC326), -2-ones (63YZ679), and -1,2-diones (63YZ679; 69GEP1901262, 69IJC833; 70JMC516; 71BRP1251821; 96MIP2). In this way, the enantiomers of perhydropyrido[1,2-*a*]pyrazine were also prepared, starting from the enantiomers of pipecolic acid via optically active perhydropyrido[1,2-*a*]pyrazin-1-ones (69JHC181). Reduction with LiAlD<sub>4</sub> gave 3,3- and 4,4-dideuteroperhydropyrido[1,2-*a*]pyrazines from the corresponding 3- and 4-ones [72JCS(P2)1374], and 3,3,4,4-tetradeutero derivatives of 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines from 3,4-diones [94JCR(S)346]. Reduction of 2-benzoyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolin-4-ones with LAH at 80–100°C in dioxane gave 2-benzyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines, from which 2-unsubstituted 2,3,4,4*a*,5,6-hexahydro-1*H* derivatives were obtained by hydrogenation over 10% Pd-C in a 2 : 1 mixture of EtOH and AcOH (67SAP67/05764–67SAP67/05767). Reduction of perhydropyrazino-[1,2-*b*]isoquinoline-1,3-one with sodium bis(2-methoxyethoxy)aluminum hydride gave the unsubstituted perhydro derivative (83USP4381302). 3,3-Diphenylperhydropyrido[1,2-*a*]pyrazin-1-one was obtained by reduction of the 1,4-dione derivative with LAH in boiling THF (70USP3531485). Reduction of a *cis*-5-methyl-1-oxoperhydropyrido[1,2-*a*]pyrazinium salt with LAH also afforded perhydropyrido[1,2-*a*]pyrazine (73CPB1248). Perhydropyrido[1,2-*a*]pyridazine was also obtained by hydrogenation of both

pyrido[1,2-*a*]pyrazin-5-ium bromide 2-oxide and 2-bromopyrido[1,2-*a*]pyrazin-5-ium bromide over  $\text{PtO}_2$  [67JCS(C)2391]. Reduction of methyl 1-oxoperhydropyrido[1,2-*a*]pyrazine-7-carboxylates with LAH gave 7-hydroxymethylperhydropyrido[1,2-*a*]pyrazines (90MIP1; 92MIP1, 92MIP61, 92MIP8; 93MIP1, 93MIP7; 95JHC857, 95TA321). Similarly, 6-hydroxymethyl- (66JMC311; 68USP3388128), and 8-hydroxymethylperhydropyrido[1,2-*a*]pyrazine (92MIP8) were prepared from the appropriate 1-oxoperhydropyrido[1,2-*a*]pyrazinecarboxylates. 3-Benzyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline was obtained from its 4,6-dioxo derivative by reduction with a mixture LAH and  $\text{AlCl}_3$  in boiling  $\text{Et}_2\text{O}$  (96TL7343). 8-Chloro-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline was prepared from its 2-oxo derivative by reduction with  $\text{BH}_3$ -THF (94MIP6; 96USP5576319). Similarly 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines were prepared from 4-oxo (84EUP107825, 84JMC995), and 3,4-dioxo derivatives (88USP4782058).

Hydrogenation of 2-bromopyrido[1,2-*a*]pyrazin-5-ium bromide and its 2-oxide over  $\text{PtO}_2$  gave pyrido[1,2-*a*]pyrazin-5-ium bromide and its 2-oxide [67JCS(C)2391]. Reduction of 7-oxo-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine with 10%  $\text{NaBH}_4$  on alumina in MeOH afforded 7-hydroxy derivative (96MIP4).

The oxo group of 7-(4-chlorophenyl)-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino- [2,1-*a*]isoquinolin-1-one [89H(29)359, 89JAP(K)89/31772] and 9-trifluoromethyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolin-1-one (85JMC945) was reduced to a methylene group by diborane and  $\text{BH}_3$ - $\text{Me}_2\text{S}$ , respectively. Wolff-Kishner reduction of 2-benzoyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline-4,7-diones afforded 4-oxo derivatives (76GEP2441261, 76GEP2457971). Reduction of 2-benzoyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline-4,7-one with  $\text{NaBH}_4$  gave a 7-hydroxy derivative (76GEP2441261). Perhydropyrido[1,2-*a*]pyrazine-1,4-diones were reduced with  $\text{AlH}_3$  to perhydropyrido[1,2-*a*]pyrazines in THF at  $0^\circ\text{C}$  (93BMC1233).

Reduction of 2-benzyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-1-one (73CPB1248) and 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*b*]isoquinolinium bromide (73CPB2039) with  $\text{NaBH}_4$  yielded perhydropyrido[1,2-*a*] pyrazin-1-one and 1,3,4,6-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one, respectively.

The 4-oxo group of both epimers of 3-benzylperhydropyrido[1,2-*a*]pyrazine-1,4-dione was regioselectively reduced when the 1-oxo group was alkylated with trimethyloxonium tetrafluoroborate, and the 1-methoxy-4-oxo-3,6,7,8,9,9*a*-hexahydro-4*H* derivative formed was then treated with  $\text{BH}_3$ -THF. The 1-oxo group was regained from 2-benzyl-1-methoxy-3,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]pyrazine to give verruculotoxin (**23**) and its 9*a*-epimer (88S963).

A mixture of 1-oxo-3-hydroxy-2-[2-(3-indolyl)ethyl]- and 2-[(3-indolyl)ethyl]perhydropyrido[1,2-*a*]pyrazines was obtained when 2-[2-(3-indolyl)ethyl]-perhydropyrido[1,2-*a*]pyrazine-1,3-dione was reduced with diisobutylaluminum hydride (DIBAH) at  $-72^{\circ}\text{C}$  (91T1065). When  $\text{NaBH}_4$  was used instead of DIBAH in the presence of  $\text{CuCl}_2$ , the 1-oxo-3-hydroxy-2-[2-(3-indolyl)ethyl] derivative was accompanied by the isomeric 3-oxo-1-hydroxy-2-[2-(3-indolyl)ethyl]perhydropyrido[1,2-*a*]pyrazine.

Reduction of 5-methyl-1-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazinium iodide, its 2-benzyl derivative and *cis*- and *trans*-5-methylperhydropyrido[1,2-*a*]pyrazin-1-ones with Li in liquid  $\text{NH}_3$  gave 1-methyldecahydro-1,5-diazecin-5-one (73CPB1248). Under the same conditions, 2-benzoyl-5-methylperhydro-pyrido[1,2-*a*]pyrazinium iodide afforded 2-benzylperhydropyrido[1,2-*a*]pyrazine. The 10-membered 1-methyldecahydro-1,5-diazecin-5-one was also obtained from *trans*-5-methylperhydropyrido[1,2-*a*]pyrazin-1-one by treatment with sodium amalgam in aqueous EtOH.

Reduction of 11-phenyl-3,4-dihydro-6*H*-pyrazino[1,2-*b*]isoquinolin-6-one with  $\text{NaBH}_3\text{CN}$  in MeOH in the presence of AcOH yielded 1,2,3,4-tetrahydro derivative (94EUP585913).

Oxidation of 9-hydroxy-5,6-dihydro-8*H*-pyrido[1,2-*a*]quinoxalin-8-one with  $\text{KMnO}_4$  in  $\text{H}_2\text{O}$  gave quinoxaline-2-carboxylic acid (75MI1).

### 3. Reactivity of Ring Nitrogen Atoms

The bridgehead nitrogens of different pyrido[1,2-*a*]pyrazines (73CPB1248), perhydropyrido[1,2-*a*]pyrazin-3-one (68JOC2379), 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline (64JOC326), its 1-oxo derivatives [73CPB2039; 74GEP2356999, 74JAP(K)74/72276, 74JAP(K)74/72283], and 2-acyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines (65BEP659249) were all quaternized with MeI. A dimethiodide was obtained from 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines (65BEP659249). 1,3,4,6,11,11*a*-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline hydrochloride and hydroiodide were obtained when the base reacted with  $\text{PhCH}_2\text{Cl}$  and EtI, respectively, in boiling benzene (64JOC326). The reaction of perhydropyrido[1,2-*a*]pyrazin-1-one and MeI afforded a mixture of the *cis*- and *trans*-methiodides, which were also obtained from 5-methyl-1-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazinium iodide by catalytic hydrogenation over  $\text{PtO}_2$  (73CPB1248). The *cis*-methiodide was converted into the stable *trans*-methiodide by heating at  $245^{\circ}\text{C}$  for 10 minutes (73CPB1248). A methiodide was prepared from 2-benzyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-1-one (73CPB1248).



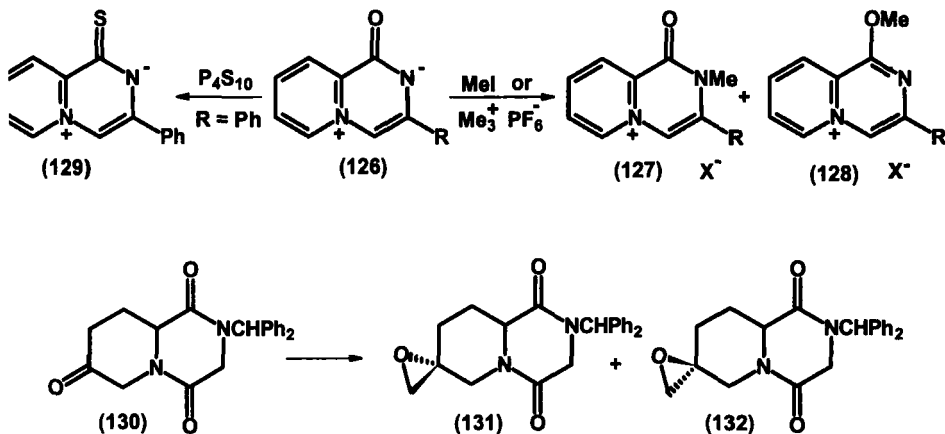
A mixture of *cis*- and *trans*-5-oxides was obtained from perhydropyrido[1,2-*a*]pyrazin-1-one and its 2-methyl derivative with 30% H<sub>2</sub>O<sub>2</sub> solution (81BAP423; 85BAP39). Treatment of N-5 oxides of perhydropyrido[1,2-*a*]pyrazin-1-one and its 2-methyl derivative with 25% NaOH gave 2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-1-ones (81BAP423). Deoxygenation of pyrido[1,2-*a*]pyrazinium-2-oxides (71JCS(C)861) and pyrazino[1,2-*b*]isoquinolin-5-ium-2-oxides [67JCS(C)2391; 72JHC177] was achieved by treatment with PCl<sub>3</sub> and PBr<sub>3</sub>, but the corresponding 1-methyl-2-oxide proved to be resistant under the same conditions [67JCS(C)2391]. Treatment of 3,5,6,7-tetrahydropyrido[1,2,3-*de*]quinoxalin-3-one-1-oxide with NaHSO<sub>3</sub>, with POCl<sub>3</sub>, or with ethyl acetoacetate and piperidine gave 3,5,6,7-tetrahydropyrido[1,2,3-*de*]quinoxalin-3-one and its 2-chloro and 3-methyl derivatives, respectively [85H(23)1729].

N-Alkylation of perhydropyrido[1,2-*a*]pyrazines and their 1-ones occurred smoothly at position 2 by the use of a variety of reagents: alkyl halides [66JMC311; 68BRP1125112, 68USP3388128; 69JHC181, 69KGS547; 71AF808; 72GEP2226063, 72YZ1339; 73CPB1248, 73YZ854; 76KFZ (4)49; 77GEP2650961, 77JAP(K)77/12188; 81BAP423; 83IJC(B)664; 85BAP39; 86JAP(K)86/53268; 91JOC5192; 93JOC690; 95JAP(K)95/33744, 95JCS(P1)369; 96MIP3], Me<sub>2</sub>SO<sub>4</sub> (67NEP6613937), 1-*p*-nitrobenzoylethylenimine (66JMC311; 68USP3388128), 3,3,3-triphenylpropyl *p*-toluenesulfonate (68BRP1125112), 1-chloro-6-fluoro- and 1,6-dichloro-3-(4-fluorophenyl)-2,3-indenes (93MIP5; 95JMC4380), CH<sub>2</sub>O (67NEP6613937), ethylene oxide (60JOC2108; 66JMC311), or a 2,2,2-trifluoroethyl ester (77JMC821). The 2-methyl derivative was prepared from **48** (R = R<sup>1</sup> = H) with MeI in the presence of NaH in DMF [72JCS(P1)2146]. The 2-methyl derivatives of 1-substituted 9-hydroxy-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazin-8-ones were obtained on treatment of the 2-unsubstituted derivatives with 37% formaldehyde solution, followed by NaBH<sub>4</sub> (78AJC187). Alkyl halides and mesylates, allyl and propargyl bromide, epoxides, alkyl vinyl ketones, alkyl acrylates, acrylonitrile, acrylamide, and 2- and 4-vinylpyridines all achieved N-alkylation of 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrido[1,2-*b*]isoquinolines [64JOC326; 67BEP698921; 75IJC230; 77IJC(B)70; 87IJC(B)761; 90JMC2970] and their 1-oxo and 6-oxo [77IJC(B)70], 1,3-dioxo (88EUP296048), and 6-oxo- and 1,6-dioxo-1,2,3,4-tetrahydro-6*H* derivatives (94EUP585913); of 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinolines (65BEP659249) and their -3-ones (86MI3) and 4-ones (86MI4; 87MI6); and of 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines [67SAP67/05765–67SAP67/05767; 69GEP1901262; 70JMC516; 72JMC351; 80IJC(B)879; 81MIP1; 96MIP2].

The Escheiler–Clarke reaction of 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline and its 6-oxo derivative [73CPB2039; 77IJC(B)70], and of 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinolines

[59YZ1003; 65BEP659249; 89H(29)359] with  $\text{CH}_2\text{O}$  and  $\text{HCO}_2\text{H}$  gave the respective *N*-methyl derivatives. Reaction of 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline with cyclohexanone in the presence of  $\text{HCO}_2\text{H}$  yielded 2-cyclohexyl derivative (65BEP659249).

*N*-Alkyl derivatives were prepared from 7-phenyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline by acylation, followed by diborane reduction (84EUP107825, 84JMC995).



Methylation of pyrido[1,2-*a*]pyrazinium-1-olates **126** with the soft methyl iodide gave the *N*-methylated compound **127** either exclusively or dominant in a mixture with the *O*-methylated derivatives **128**. When a hard, positively charged trimethyloxonium salt was used, the *O*-methylated or a mixture of the *N*- and *O*-methylated derivatives **127** and **128**, with a predominance of the latter, was obtained. Phenylpyrido[1,2-*a*]pyrazinium-1-thiolate (**129**), obtained from **126** ( $\text{R} = \text{Ph}$ ) with  $\text{P}_4\text{S}_{10}$ , gave exclusively the 1-methylthiopyrido[1,2-*a*]pyrazinium salt with both methylating agents (90JHC1673). From the isomeric pyrido[1,2-*a*]pyrazinium-3-olate, only the *O*-methylated product could be isolated (90JHC1673).

Deprotonation of an 8,10-diphenyl-6-oxo-5,6-dihydropyrido[1,2-*a*]quinoxalinium salt gave the zwitterionic pyrido[1,2-*a*]quinoxalinium-6-olate [84JHC1609, 84KFZ(6)700], which underwent *N*-methylation on the action of  $\text{CF}_3\text{SO}_3\text{Me}$  (84JHC1609).

*N*-(Het)arylation of perhydropyrido[2,1-*a*]pyrazine derivatives has also been carried out with 2,5-difluorobenzonitrile and 2,5-difluoro- and 4-fluoronitrobenzene (96MIP4); with 3-chloro-1,2-benzisoxazole (92MIP6, 92MIP8; 93MIP1, 93MIP7; 95JHC857, 95TA321); with 3,6-dichloro-1,2-benzisoxazole (92MIP6, 92MIP8); with 3-chloro-1,2-benzisothiazole (92MIP6, 92MIP8); with 2-halopyridines (90MIP1; 91JOC5192; 92MIP1; 94T1811; 96MIP4); with 2,6-dimethoxypyridine (96MIP4); with 2-chloropyr-

rimidines (90MIP1; 92MIP1; 96MIP4); with 2-chloropyrazines (82 USP4339579; 96MIP4); with 3,6-dichloropyridazine (96MIP4); with 8-chloro-11,10-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one in the presence of  $\text{TiCl}_4$  (81EGP151166; 84PHA812; 86URP1015618); with 8,11-dichlorodibenz[*b,f*]-1,4oxazepine (96MIP7); with 7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids [84JAP(K)84/137481; 85JAP(K)85/23382]; with 10-fluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids [83JAP(K)83/225092; 84JAP(K)84/219293]; and with 3-dichloro-2*H*-1,2,4-benzothiadiazin-1,1-dioxides (79GEP2757925; 81AF 279). All-*cis* perhydropyrazino[1,2-*b*]isoquinoline (83USP4381302), and 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (70JMC516) were N-arylated with 2-halopyridines and 4-chloro-3-nitropyridine, respectively. 1,2,3,6,7,11*b*-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline was N-arylated with 4-chloro-2-phenylquinazoline (96BRP2295387), and 6-chloro-9- $\beta$ -D-ribofuranosylpurine derivatives (73GEP2139107). A 2-phenyl derivative was obtained from 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline with  $\text{PhCl}$  in the presence of  $\text{Na}$  (65BEP659249).

Reaction of 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline with  $\text{H}_2\text{NCN}$ ,  $\text{KCNO}$  in 5%  $\text{HCl}$ , and  $\text{MeCN}$  in the presence of  $\text{AlCl}_3$  gave the 2-amidine, aminocarbonyl, and 2-(1-iminoethyl) derivatives, respectively (65BEP659249). A 2-substituted derivative was also obtained from the reaction of 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one and 3-methyl-5-nitro-2-furaldehyde oxime (84MI1).

N-Acylation of perhydropyrido[1,2-*a*]pyrazines was performed with acyl halides, carboxylic anhydrides [61BSF2135; 69KGS547; 73CPB1248; 78GEP2748260; 81KFZ(8)55; 92MIP6; 94MIP2, 94T1811, 94USP5354747], phenyl isothiocyanate (68JOC2379), (3,4-dichlorophenyl)acetic acid in the presence of DDC (93JMC2311; 94MIP2), cyclohexylacetic acid in the presence of 1-hydroxybenzotriazole and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (92MIP6, 92MIP8), 8-chloro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine-10-carbonyl chloride (94MIP7, 94USP5354747; 95USP5461047), di-*tert*-butyl dicarbonate (93MIP7), benzyl chloroformate (92MIP6, 92MIP8), ethyl chloroformate (93JOC690), *N,N*-diethylcarbamoyl chloride [83IJC(B)664], iso(thio)cyanates (59CB240; 60JOC2108; 66JMC311), and 2,2,2-trifluoroethyl 2,5-bis-(2,2,2-trifluoroethoxy)benzoate (77JMC821). 1,2,3,4-Tetrahydropyrido[1,2-*a*]pyrazinium chloride was N-acylated with an active ester of 4-[[2-carboxy-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hepten-3-yl]thio]-2-pyrrolidinecarboxylic acid [95JAP(K)95/101959]. Acyl chlorides, acid anhydrides,  $(\text{PhCO})_2\text{O}$ , esters, alkyl iso(thio)cyanates, sulfonic acid, chloroformates, and carboxylic acids in the presence of DCC, or  $\text{PCl}_3$ , or  $\text{SOCl}_2$ , or  $\text{SiCl}_4$  all caused N-acylation of 2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinolines [64JOC326; 77IJC(B)70; 90IJC(B)455]

and their 6-oxo derivative [77IJC(B)70]; 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines (65BEP659249; 84EUP107825, 84JMC995; 86MI4) and their 3-oxo (86MI3), 4-oxo [75GEP2331713, 75GEP2362539; 76GEP2441261; 82GEP3324532; 83H (20)1731; 84GEP3316928; 85CB4620, 85KGS798, 85USP4497952; 86JHC189; 87MI6; 88MI13; 89AP(322)795; 91AP(324)235, 91MI14; 96AF207, 96MI9], 4-thione (76GEP2441261), and 3,4-dioxo derivatives (85MI1); 2,3,4,4*a*,5,6-hexahydro-1*H*- (47HCA920; 67SAP67/05764, 67SAP67/05767; 69GEP1901262, 69IJC833; 70JMC516), and perhydropyrazino[1,2-*a*]quinolines (64JOC326; 85MI1); 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline and its 1-oxo (88MI13), and 1,2-dioxo derivatives (85MI1); and 5,6-dihydro-8*H*-pyrido[1,2-*a*]quinoxalin-8-ones (75MI1). Reaction of 9-hydroxy-5,6-dihydro-8*H*-pyrido[1,2-*a*]quinoxalin-8- one with Ac<sub>2</sub>O gave the 5-acetyl-9-acetoxy derivative (75MI1; 86MI10). N-Deacylation of 3-benzoyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolin-1-one (85MI1), 2-benzoyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline (65BEP659249), and 2-acyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones (76GEP2441261, 76GEP 2508947; 77GEP1795728; 84GEP3316928) was achieved under acidic conditions.

2-Ethoxycarbonylperhydropyrido[1,2-*a*]pyrazines were obtained from the 2-benzyl derivatives by reaction with ClCOOEt in CH<sub>2</sub>Cl<sub>2</sub> at 0°C, then with aqueous K<sub>2</sub>CO<sub>3</sub> [93JOC690; 95JCS(P1)369]. The 2-guanyl derivative was obtained from perhydropyrido[1,2-*a*]pyrazine on treatment with 1-guanyl-3,5-dimethylpyrazole nitrate (69JHC181). The *N*-dithiocarboxylic acid and (*N*-methylthio)thiocarbonyl derivatives were prepared from 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*b*]isoquinoline with CS<sub>2</sub> in the absence and in the presence of MeI, respectively (69T725). The *N*-nitroso derivatives were obtained in the reaction of perhydropyrido[1,2-*a*]pyrazine (85EUP135837, 85USP4551450), 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (87MI6), 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*b*]isoquinoline [71JPR(313)825], and 2,3,4,4*a*,6,7-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (47HCA920) with NaNO<sub>2</sub> in acidic media.

Reaction of 1-(3,4-dimethoxybenzyl)-9-hydroxy-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazin-8-one with 37% formaldehyde solution gave a tetracyclic tetrahydroprotoberberine analogue in a Mannich-type reaction (78AJC187). Reactions of 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines with 1*H*-pyrrolo[2,3-*b*]pyridine in the presence of 37% aqueous CH<sub>2</sub>O and AcONa in AcOH, and with 3-dimethylaminomethyl-1*H*-pyrrolo[2,3-*b*]pyridine afforded 3-[(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl] derivatives (94MIP6; 96USP5576319).

2-Unsubstituted perhydropyrido[1,2-*a*]pyrazines were obtained by hydrolysis of the 2-(4-nitrosophenyl) (59CB1510), 2-*tert*-butoxycarbonyl (96MIP4), and 2-ethoxycarbonyl derivatives [93JOC690; 95JCS(P1)369].

Treatment of (3*S*,9*aS*)-*cis*-3,9*a*-H-3-benzyl-2-tosylperhydropyrido[1,2-*a*]-pyrazin-1-one with naphthalene-sodium gave verruculotoxin (**23**) (91 TL1417). N-Demethylation of 2-methyl-7-phenyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline occurred on treatment with methyl chloroformate in CHCl<sub>3</sub> in the presence of NaHCO<sub>3</sub> and, after work-up, treatment of the oily residue with 95% hydrazine and then with 50% NaOH (84EUP107825, 84JMC995). 2-Unsubstituted perhydropyrido[1,2-*a*]-pyrazines were obtained from 2-benzyl derivatives (94T1811; 96MIP3) and the 2-benzyloxycarbonyl derivative (92MIP6, 92MIP8) by catalytic hydrogenation over Pd-C and Pd(OH)<sub>2</sub>-C, respectively. 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (96MIP2), and 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[1,2-*a*]isoquinolin-4-one (86JHC189) were obtained from the respective *N*-benzyl derivatives by catalytic hydrogenation over Pd-C.

*N*-Acyl derivatives of 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines [83H(20)1731], their 4-oxo derivatives (75GEP2331713; 76 GEP2508947), 2,3,4,4*a*,5,6-hexahydro-4*H*-pyrazino[1,2-*a*]quinolin-1-one (85MI1; 87MI6), and 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline (83 KGS677) were deacylated on acidic hydrolysis.

The treatment of 8*H*-pyrido[1,2-*a*]quinoxalin-8-ones with a Grignard reagent gave 6-substituted 5,6-dihydro derivatives, which could be dehydrogenated to 6-substituted 8*H*-pyrido[1,2-*a*]quinoxalin-8-ones (35CB 1716).

#### 4. Reactivity of Ring Carbon Atoms

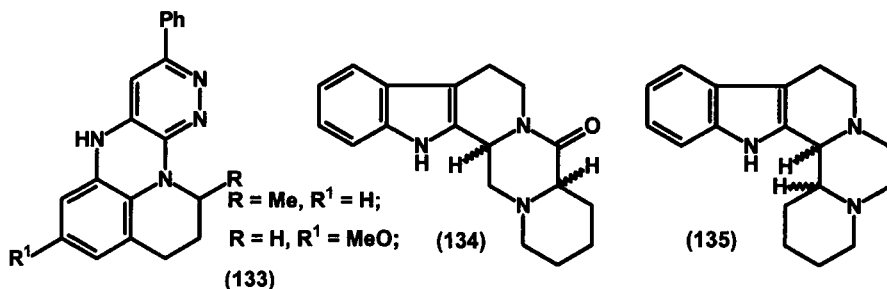
2,3,4,6,7,8-Hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-1-ones were prepared by oxidation of 2-substituted perhydropyrido[1,2-*a*]pyrazines and perhydropyrido[1,2-*a*]pyrazin-1-one with Hg(OAc)<sub>2</sub> in 5% aqueous AcOH (73CPB1248). Oxidation of 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline with Hg(OAc)<sub>2</sub> in 5% aqueous AcOH gave the 6-oxo derivative [73CPB2039; 77IJC(B)70]. 1,3,4,6,11,11*a*-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one under these conditions afforded the 6-hydroxy-1,3,4,6-tetrahydro-2*H* derivative, which on treatment with HBr gave 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*b*]isoquinolinium bromide (73 CPB2039). From the latter, 6-hydroxy-1,3,4,6-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one was obtained by treatment with K<sub>2</sub>CO<sub>3</sub>. Air oxidation of 1,2,3,4-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinolin-1-one in the presence of MeI in acetone also gave the 6-hydroxy derivative. Under N<sub>2</sub> no reaction occurred. A mixture of 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one and 6-hydroxy-1,3,4,6-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one was obtained when 1,3,4,6-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one was heated in 10% HCl (73CPB 2039).

Dehydrogenation of 2-acyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones with sulfur gave the 2,3,6,7-tetrahydro derivatives [75GEP2418111; 89AP(322)795; 91KFZ(9)85]. Oxidation of 2-cyclohexylcarbonyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one with DDQ gave the 6,7-dihydro-4*H* derivative [89AP(322)795]. 1-Oxo-1,2,3,4,6,7,8,9-octahydropyrido[1,2-*a*]pyrazinium perchlorate was obtained with HClO<sub>4</sub> from both 2,3,4,6,7,8-hexahydro-1*H*-pyrido-[1,2-*a*]pyrazin-1-one and 9*a*-cyanoperhydropyrido[1,2-*a*]pyrazin-1-one (73CPB1248). The latter was obtained from the quaternary perchlorate salt with NaCN.

When the 7-enolate anion of 2-benzylperhydropyrido[1,2-*a*]pyrazin-6-one, generated with LDA or BuLi in THF, was treated with benzophenone and its 4,4'-difluoro derivative, a mixture of diastereomeric *cis*- and *trans*-7-diarylhydroxymethyl derivatives was formed, which was dehydrated with 48% aqueous HBr (93JOC690).

A 1:1 mixture of *cis*- and *trans*-2,3-dimethyl-3-ethylthioperhydropyrido[1,2-*a*]pyrazine-1,4-diones was obtained from the 3-hydroxy-2,3-dimethyl derivative on treatment with EtSH in the presence of ZnCl<sub>2</sub> (74CB2804).

The 8-oxo group of 1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazine-1,8-diones was condensed with CH-acid compounds [71AP(304)342]. Reaction of the oxo group of 2-benzylperhydropyrido[1,2-*a*]pyrazin-7-one with PhCH<sub>2</sub>PO(OEt)<sub>2</sub> in the presence of NaH in 1,3-dimethylimidazolidin-2-one at 5°C gave a 3:1 mixture of *E*- and *Z*-isomers of the 7-benzylidene derivatives [95JCS(P1)369]. Grignard reaction of 2-substituted perhydropyrido[1,2-*a*]pyrazin-7-one with (het)arylmagnesium bromides afforded a diastereomeric mixture of 7-hydroxy-7-(het)aryl derivatives, which was dehydrated on treatment with 48% aqueous HBr at 90–100°C to give a mixture of 2-substituted 7-(het)aryl-2,3,4,6,9*a*- and -2,3,4,8,9,9*a*-hexahydro-1*H*-pyrido[1,2-*a*]pyrazines (94T1811).



The 7-oxo group of perhydropyrido[1,2-*a*]pyrazine-1,4,7-trione **130** was converted into an epoxide group with trimethylsulfonium iodide in the presence of *tert*-BuOK in DMSO, and the separated epoxides **131** and **132**

reacted with adenine in the presence of  $K_2CO_3$  in DMF at  $100^\circ C$  (93BMC1233).

Treatment of 3-hydroxy-2,3-dimethylperhydropyrido[1,2-*a*]pyrazine-1,4-dione with ethanethiol in  $CHCl_3$  in the presence of  $ZnCl_2$  gave the 3-ethylthio derivative (74CB2804). Heating 1-imino-1,4-dihydropyrido[1,2-*a*]pyrazin-5-ium bromide in 48% HBr gave 1-oxo-1,2-dihydropyrido[1,2-*a*]pyrazin-5-ium bromide [67JCS(C)2391].

Pyrido[1,2-*a*]pyrazin-5-ium bromide 2-oxide was brominated with  $Br_2$  in 48% HBr to give the 1-bromo derivative [67JCS(C)2391]. Bromination of 5,6*a*,7,8,9,10-hexahydro-6*H*-pyrido[1,2-*a*]quinoxalin-6-one with  $Br_2$  in AcOH occurred at position 3, whereas nitration in conc.  $H_2SO_4$  with  $KNO_3$  occurred at position 2 [88JCS(P1)1997]. Nitration of 8-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines gave 9-nitro derivatives (69GEP1901262; 71BRP1251821; 74USP3829573), sometimes containing a small amount of the 7-nitro isomer (72JMC351). 7-Phenyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline under similar conditions afforded the 10-nitro-7-(4-nitrophenyl) derivative, whereas regioselective nitration in anhydrous  $CF_3COOH$  gave the 7-(4-nitro) derivative (84EUP107825, 84JMC995). The nitro group on a phenyl ring was hydrogenated over Pd-C to an amino group, which was converted via its diazonium salt into a chlorine atom and a hydroxy group. The latter was methylated by treatment with diazomethane (84EUP107825, 84JMC995).

Electrophilic substitution (bromination, nitration) of 2-substituted 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones occurred on the aromatic moiety to give either 11- or 8-substituted derivatives; the site was not determined (76GEP2441261). The nitro group was reduced to an amino group, which was alkylated, acylated, and converted to different groups via a diazonium group, and involved in diazonium coupling.

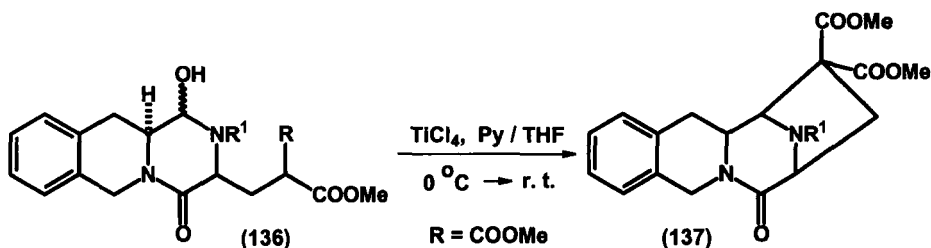
Treatment of 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline-1,4-diones with  $Et_3OBF_4$  in the presence of  $Na_2CO_3$  gave regioselectively 1-ethoxy-3,4,11,11*a*-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinolin-4-ones, which were alkylated at position 3 at  $-78^\circ C$  in the presence of LDA with cinnamyl chloride and propargyl bromide to give 3-substituted 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline-1,4-diones (85TL2955).

The Mannich reaction of praziquantel (**24**) and amines in the presence of formaldehyde gave 3-aminomethyl derivatives (88MI11).

Treatment of 2-benzoyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one with  $NaNH_2$ , then with ethylene oxide yielded the 3-(2-hydroxyethyl) derivative (76GEP2441261). 4-Thioxo and 2-(cyclohexylthiocarbonyl)-4-thioxo derivatives were prepared from 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one and its 2-cyclohexylcarbonyl derivative by treatment with  $P_4S_{10}$ .

Reaction of 9-hydroxy-2-methyl-6-phenyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline, prepared from its 9-methoxy derivative in 48% HBr, with 5-chloro-1-phenyl-1*H*-tetrazole in the presence of  $K_2CO_3$  in DMSO yielded the 9-(1-phenyl-1*H*-tetrazol-5-yloxy) derivative, which then gave its 9-unsubstituted derivative by hydrogenation over 5% Pd-C (88USP4782058).

The reaction of 2-benzoylmethyl-3,5,6,7-tetrahydropyrido[1,2,3-*de*]-quinoxalin-3-ones with  $H_2NNH_2$  and subsequent cyclization of the reaction products in AcOH gave tetracyclic compounds **133** [78KFZ(7)89]. Heating 1-oxo-3-hydroxy-2-[2-(3-indoyl)ethyl]perhydropyrido[1,2-*a*]-pyrazine and the isomeric 1-hydroxy-3-oxo derivative in conc. HCl gave a mixture of *cis* and *trans* pentacyclic derivatives **134** and **135** (91T1065).

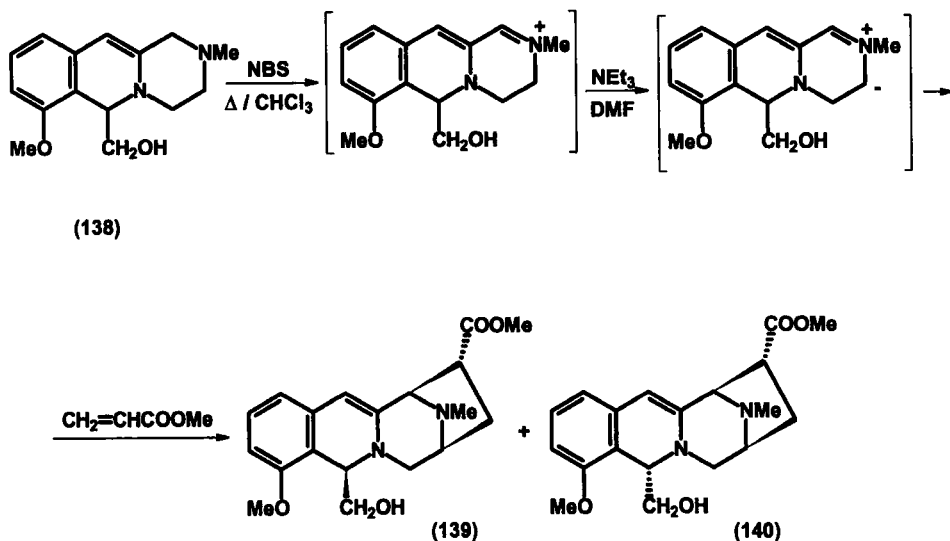


Treatment of a diastereomeric mixture of 1-hydroxy-3-[2,2-bis(methoxycarbonyl)ethyl]-1,2,3,6,11,11*a*-hexahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-ones (**136**,  $R = \text{COOMe}$ ) with  $TiCl_4$ -pyridine afforded the tetracyclic derivatives **137** [85JAP(K)85/258182; 87TL4065]. Cyclization of the monoesters **136** ( $R = H$ ) was unsuccessful.

Treatment of 2-substituted 3*H*-pyrido[1,2,3-*de*]quinoxalinium bromides with  $NEt_3$  afforded *anhydro*-3*H*-pyrido[1,2,3-*de*]quinoxalinium hydroxides, which reacted stereoselectively at positions 3 and 5 with acetylenic and olefinic dipolarophiles to give tetra- and pentacyclic heterocycles [80CL951, 80H(14)1107; 89JCS(P1)945]. A similar cycloaddition occurred between 1,2-bis-methoxycarbonylpyrido[1,2,3-*de*]quinoxalinium ylide [87 JCS(P1)403], 2-substituted pyrido[1,2,3-*de*]quinoxaline mesomeric betaines [89JCS(P1)945, 89JCS(P1)965], and olefinic dipolarophiles. The cycloadducts sometimes underwent an acid-catalyzed retro-Michael reaction [89JCS(P1)965]. Cycloaddition of pyrazino[1,2-*b*]isoquinolinium perchlorates and their 2-oxides with nucleophilic alkenes occurred readily across the *meso* positions of the central ring (72JHC177).

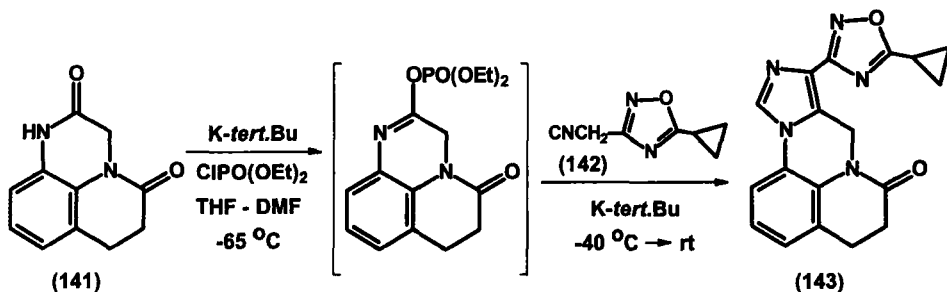
Acidic hydrolysis of 11-cyano-6-imino-6*H*-pyrido[1,2-*b*]isoquinoline through protonation of the imino group gave the 6-oxo-6*H* derivative (78JOC3536).





Treatment of 6-hydroxymethyl-2-methyl-7-methoxy-1,2,3,4-tetrahydro-6H-pyrazino[1,2-*b*]isoquinolin-4-one (**138**) with NBS, then with methyl acrylate in the presence of  $\text{NEt}_3$  afforded a 1 : 5 diastereomeric mixture of tetracyclic derivatives **139** and **140** (95JOC6791). Reductive radical decyanation of 3-methyl-5,5-dicyano-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline with a mixture of  $\text{Bu}_3\text{SnH}$  and 2,2'-azobisisobutyronitrile afforded nearly a 1 : 1 mixture of diastereomers of the 5-cyano derivative (95TL5159).

The 9,10-difluoro-7-oxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylic acids could be regioselectively replaced by cyclic amines at position 10 (94EUP614664). 9- or 10-Unsubstituted, 9-chloro-, 10-chloro, 9-iodo, 10-iodo, and 9-cyano derivatives were prepared from 9-bromo- and 10-bromo-5-methoxycarbonylmethyl-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,3-dione by hydrogenation over Pd-C in a mixture of THF and AcOH, by treatment with  $\text{CuCl}$  in DMSO at  $160^\circ\text{C}$ , and with KI and  $\text{CuI}$  in HMPA at  $160^\circ\text{C}$ , and  $\text{CuCN}$  in DMSO at  $180^\circ\text{C}$  (93MIP2; 94CP2121609, 94EUP627434; 95BMC1533). The 9-nitro derivative was prepared by nitration of 5-methoxycarbonylmethyl-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,3-dione with *i*-Pr $\text{NO}_3$  in conc.  $\text{H}_2\text{SO}_4$  at  $0^\circ\text{C}$  (93MIP2). Tetracyclic compound **143** was prepared from 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,5-dione (**141**) by reaction with diethyl chlorophosphate and then 1,2,4-oxadiazol **142** (96JMC4654, 96USP 5541324).



### 5. Reactivity of Substituents Attached to Ring Carbon Atoms

Ester, ethoxycarbonylmethyl, nitrile, and cyanomethyl or 2-nitrovinyl groups on the pyrido[1,2-*a*]pyrazine skeleton were reduced with LAH to hydroxymethyl, 2-hydroxyethyl, aminomethyl, and 2-aminoethyl groups, respectively (57N62; 59CB240; 66JMC311; 69JHC181; 92MIP6, 92MIP8; 93MIP1, 93MIP7; 95TA321). A 7-(2-aminomethyl) derivative was also obtained by hydrogenation of a 7-(azidomethyl) derivative over Pd-C (90MIP1; 92MIP1, 92MIP6, 92MIP8) and from (phthalimido)methyl derivatives with anhydrous hydrazine. The amino group was acylated (92MIP8; 93MIP7; 94TA211), converted to a guanidino group (69JHC181), and reacted with 3,3-tetramethylene- and 4,4-tetramethyleneglutaric anhydrides, succinic anhydride, and other similar anhydrides in toluene or xylene, sometimes in the presence of  $\text{Ac}_2\text{O}$  (90MIP1; 92MIP1, 92MIP6, 92MIP8; 93MIP1, 93MIP7; 95TA321). 7-(Succinimidomethyl) (90MIP1; 92MIP1) and 7-[(het)aryloxy]methyl derivatives (96MIP4) were also prepared from 7-hydroxymethyl-2-substituted perhydropyrido[1,2-*a*]pyrazines by treatment with succinimide and the appropriate phenol in the presence of  $\text{PPh}_3$  and diethyl azodicarboxylate (90MIP1; 92MIP1). The 7-aminomethyl side chain on a perhydropyrido[1,2-*a*]pyrazine skeleton was converted into an acetoxymethyl group by treatment with isoamyl nitrite in  $\text{AcOH}$ , and an acetoxymethyl group was hydrolyzed to a hydroxymethyl group (90MIP1; 92MIP1). A 2-hydroxyethyl side chain gave the 2-(1-pyridinium)ethyl group on treatment with tosyl chloride in pyridine (60JOC2108). Nitrosation of 2-phenylperhydropyrido[1,2-*a*]pyrazine with  $\text{NaNO}_2$  in 5N HCl gave the *p*-nitrosophenyl derivative (59CB1510). The nitro groups of 2-[2-(4-nitrobenzamido)ethyl]-6-methyl- (66JMC311), 2-(4-nitrobenzoyl)perhydropyrido[1,2-*a*]pyrazine [81KFZ(8)55], and 3-(3-nitro-4-pyridyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (70JMC516) were catalytically hydrogenated over Pt or Raney Ni. The amino group of 2-amino-perhydropyrido[1,2-*a*]pyrazines and 3-amino-2,3,4,4a,5,6-hexahydro-1*H*- and 3-aminoperhydropyrazino[1,2-*a*]quinolines was condensed with 3-

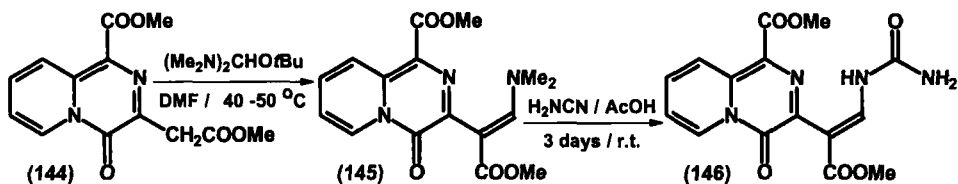
formylrifamycin SV (85EUP135837, 85USP4551450; 90JMC552). The hydroxy group of 2-(3-hydroxypropyl)-7-methoxy-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazin-8-one was acylated with diphenylacetyl chloride (61USP2999860). A side-chain hydroxy group was acylated on the perhydropyrido[1,2-*a*]pyrazine skeleton with PhNCO (59CB240).

Reaction of 2-(benzisoxazol-3-yl)-7-[2-(3,3-tetramethyleneglutarimido)ethyl]perhydropyrido[1,2-*a*]pyrazine with sodium bis(trimethylsilyl)amide in THF at  $-70^{\circ}$ , then with (+)-(camphorsulfonyl)oxaziridine gave a diastereomeric mixture of 7-[2-(2*a*-hydroxy-3,3-tetramethyleneglutrimido)ethyl] derivatives (93MIP1).

The 7-oxo group was liberated from 7-ethylenedioxy-2-substituted perhydropyrido[1,2-*a*]pyrazines on heating in boiling 6 N HCl (91JOC5192; 94T1811; 96MIP4). The 2-unsubstituted 7-oxo derivative could not be prepared similarly due to its unstable nature.

Treatment of 2-(5-fluoro-4-methylthio-2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazines with Raney Ni in boiling EtOH gave 2-(5-fluoro-2-pyrimidinyl) derivatives (96MIP4). Dehalogenation occurred when a 2-(2-chloro-4-pyrimidinyl), 2-(6-chloro-3-pyridazinyl)perhydropyrido[1,2-*a*]pyrazines (96MIP4), and 2-benzoyl-7-chloro-9-methyl-1,2,3,6,7,11*b*-pyrazino[2,1-*a*]isoquinolin-4-one (76GEP2441261, 76GEP2457971) were hydrogenated over 10% Pd-C. The bromo atom of a 2-(5-bromo-2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine was exchanged for a fluoro atom by treatment with *n*-BuLi and *N*-fluorodibenzenesulfonamide in a 4:1:1 mixture of THF-hexane-Et<sub>2</sub>O at  $-100^{\circ}\text{C}$  (96MIP4). Oxidation of 7-(4-fluorophenylthio)methyl-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine with *m*-CPBA in CHCl<sub>3</sub> gave the 7-(4-fluorophenylsulfonyl) derivative. The 7-phenoxy derivative was obtained from 7-hydroxy-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine by treatment with phenol in the presence of PPh<sub>3</sub> and diethyl azodicarboxylate in MeOH at ambient temperature. Reactions of 7-cyanomethyl-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine with 1*M* DIBAH at room temperature for 2 h, then at  $50^{\circ}\text{C}$ , followed by treatment with 2 N HCl, and then with 4-fluorophenyl magnesium bromide gave an epimeric mixture of 7-[2-(4-fluorophenyl)-2-hydroxyethyl] derivatives. Treatment of the 7-cyanomethyl derivative with 4-fluorophenyl magnesium bromide in the presence of CuBr in boiling THF gave the 7-(4-fluorobenzoyl)methyl derivative after treatment of the reaction mixture with 15% H<sub>2</sub>SO<sub>4</sub> (96MIP4). Oxidation of 7-[(4-fluorophenyl)hydroxymethyl]-2-substituted perhydropyrido[1,2-*a*]pyrazines with oxalyl chloride and DMSO yielded 7-(4-fluorobenzoyl) derivatives (96MIP3, 96MIP4). Methylation of a 7-(5-fluoro-1*H*-indol-3-yl)methyl-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine with MeI in DMF in the presence of NaH afforded its 7-(5-fluoro-1-methyl-1*H*-indol-3-yl)methyl derivative (96MIP4).

Reaction of methyl 2-(1-methoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]-pyrazin-3-yl)acetate (**144**) with *tert*-butoxybis(dimethylamino)methane furnished 3-dimethylaminoacrylate **145** (96JHC639). Urea **146** was obtained from **145** with cyanamide.



The carboxylic group of 4-oxoperhydropyrido[1,2-*a*]pyrazine-6-carboxylic acid was esterified with MeOH (66JMC311). A side-chain alkoxy-carbonyl group on perhydropyrido[1,2-*a*]pyrazine (59CB1510), and 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline skeletons (70JMC516) was hydrolyzed. The carboxylic acids obtained from 2-substituted 7-oxo-perhydropyrido[1,2-*a*]pyrazine-6- and -8-carboxylates [92JCS(P1)1035], from 6-oxo-5,6-dihydro-8*H*-pyrido[1,2-*a*]quinoxaline-10-carboxylate derivatives [66AP(299)139], and from 1,8-dioxo-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazine-6-carboxylic acid (65ZOR2222) were decarboxylated. Saponification of 7-oxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylates afforded 6-carboxylic acids [80JAP(K) 80/49379; 82USP4348521; 87USP4636506; 89GEP3913245; 93BMC1711]. Treatment of *cis*-1-methoxy-9*a*-methyl-3-isopropyl-3,6,9,9*a*-tetrahydro- and 3,6,7,8,9,9*a*-hexahydro-4*H*-pyrido[1,2-*a*]pyrazin-4-ones with 3 N HCl and immediate work-up gave ring-opened products, but when a longer reaction period was applied in the case of the hexahydro derivative, ring closure took place to give *cis*-3-isopropyl-9*a*-methylperhydropyrido[1,2-*a*]pyrazine-1,4-dione (88LA1025). The 9-acyloxy group of 2-(diphenylacetyl)-9-(diphenylacetoxy)-1-(2-tetrahydrofuryl)perhydropyrido[1,2-*a*]pyrazine was hydrolyzed with KOH in EtOH (61BSF2135). The ethoxymethyl group of 3-ethoxymethylperhydropyrido[1,2-*a*]pyrazine was converted into a hydroxymethyl group by treatment with 48% HBr (59CB240). Acidic hydrolysis of 2-[2-(4-nitrobenzamido)ethyl]-6-methylperhydropyrido[1,2-*a*]pyrazine yielded its 2-(2-aminoethyl) derivative (66JMC311).

The halogen atom of 2-( $\omega$ -haloalkyl)-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,3-diones was replaced by 4-substituted piperazines (88EUP296048; 90EUP378468).

Heterocyclic ring nitrogen, a hydroxy group, and a carbon atom of CH acids were alkylated with 2-(2-chloroethyl) and 2-(3-chloropropyl)perhydropyrido[1,2-*a*]pyrazine [71GEP2029185, 71JPP71/34717, 71JPP71/43795;

72FRP2092785, 72GEP2226063; 73URP367102; 74JAP(K)74/28755; 75 JAP(K)75/23039].

Hydrolysis of a side-chain acetamido group on perhydropyrido[1,2-*a*]-pyrazine (78GEP2748260), and 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline [871JC(B)761] gave an amino group. The amino group was converted into the dimethylamino group on treatment with CH<sub>2</sub>O in the presence of Pd-C under H<sub>2</sub> in EtOH [871JC(B)761]. Acidic hydrolysis of a 2-*p*-nitrobenzamidoethyl group on perhydropyrido[1,2-*a*]pyrazine gave a 2-aminoethyl group (68USP3388128). Hydrolysis of a side-chain nitrile group on perhydropyrido[1,2-*a*]pyrazines in conc. H<sub>2</sub>SO<sub>4</sub> gave carboxamide derivatives (72GEP2226063). Esterification of 1-oxoperhydropyrido[1,2-*a*]pyrazine-6-carboxylic acid in MeOH saturated with HCl gave the methyl ester (68USP3388128).

Nitration of 3-phenylperhydropyrido[1,2-*a*]pyrazin-1-one with 90% HNO<sub>3</sub>-conc. H<sub>2</sub>SO<sub>4</sub> yielded the 3-(4-nitrophenyl) derivative (67NEP 661393). The amino group of 3-amino-5,6*a*,7,8,9,10-hexahydro-6*H*-pyrido[1,2-*a*]quinoxalin-6-one, obtained from the 3-nitro derivative by reduction with Sn in conc. HCl, was deaminated via its diazonium salt by Cu treatment (83JHC1509). Catalytic reduction of 2-(2-nitrophenyl)perhydropyrido[1,2-*a*]pyrazines over 10% Pd-C afforded 2-(2-aminophenyl) derivatives (96MIP4). The amino group was changed to a hydrogen atom with 97% isoamyl nitrite in THF. The 9-chloro derivative was obtained by diazotiation of 9-amino-8-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline, prepared from its 9-nitro derivative by catalytic hydrogenation over 10% Pd-C and treatment of the diazonium salt with CuCl (69GEP1901262). The amino group of 3-(4-aminobutyl)-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline was acylated with acyl chlorides (96MIP9).

Reduction of the oxo group of the cyclohexanone moiety of 2-(4-oxocyclohexylcarbonyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one with K-selectride in THF at -70°C gave the *trans*-4-hydroxycyclohexyl derivative [91AP(324)235], and a 3:1 mixture of the *cis*- and *trans*-4-hydroxycyclohexyl derivatives was obtained with NaBH<sub>4</sub> [76GEP2441261, 76GEP2457971; 91AP(324)235]. The 4-oxocyclohexylcarbonyl group was also catalytically reduced to the 4-hydroxycyclohexylcarbonyl group over Raney Ni (76GEP2441261; 84GEP3316928), and it was converted into the 4,4-difluorocyclohexylcarbonyl group by treatment with SF<sub>4</sub> (76GEP2441261). A side-chain carbonyl group in 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline [67SAP67/05767; 70JMC516; 80IJC (B)879] and 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline skeletons (75IJC230) was reduced to a hydroxymethylene group with NaBH<sub>4</sub>. The hydroxy group was acylated with Ac<sub>2</sub>O (67SAP67/05767). A

side-chain carbonyl group in 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]-quinoline reacted with Grignard reagents (67SAP67/05767; 70JMC516).

Reduction of 2-[2-(3,4-dichlorophenyl)acetyl]perhydropyrido[1,2-*a*]-pyrazine with freshly prepared  $\text{AlH}_3$  afforded the 2-[2-(3,4-dichlorophenyl)ethyl] derivative (93JMC2311; 94MIP2). The 7-formyl group of a perhydropyrido[1,2-*a*]pyrazine was reduced with  $\text{NaBH}_4$  to a hydroxymethyl group, which was oxidized to a formyl group with  $\text{SO}_3$ -pyridine in a mixture of DMSO and  $\text{CH}_2\text{Cl}_2$  in the presence of Hunig's base (93MIP7; 95TA321), with  $(n\text{-Pr})_4\text{NRuO}_4$  in the presence of *N*-methylmorpholine-*N*-oxide and 4-Å molecular sieves (96MIP4), and with a mixture of oxalyl chloride and DMSO in  $\text{CH}_2\text{Cl}_2$  at  $-50^\circ\text{C}$  (96MIP3, 96MIP4). Treatment of 7-formylperhydropyrido[1,2-*a*]pyrazines with benzyltriphenylphosphonium chloride in the presence of *n*-BuLi, and with 4-fluorophenyl magnesium bromide gave the 7-(2-phenyl)ethenyl (96MIP4) and 7-[(4-fluorophenyl)hydroxymethyl] derivatives (96MIP3, 96MIP4), respectively. The 7- and 8-hydroxymethyl groups were acylated with mesyl chloride (90MIP1; 92MIP1, 92MIP6, 92MIP8; 93MIP1, 93MIP7; 96MIP3, 96MIP4), and the mesyloxymethyl group was converted to a cyanomethyl group with NaCN (92MIP6, 92MIP8; 93MIP1, 93MIP7; 96MIP4); to an aryloxymethyl group with phenols in the presence of NaH (96MIP4); to (5-fluoro-1-indolyl)methyl, (2-oxo-2,3-dihydro-1*H*-indol-1-yl)methyl, (2-methyl-1-benzimidazolyl)methyl, and (2-oxo-2,3-dihydro-3-benzoxazolyl)methyl groups with the appropriate heterocycle in the presence of NaH (96MIP4); to a (5-fluoro-1*H*-indol-3-yl)methyl group with 5-fluoroindole in the presence of EtMgBr (96MIP4); to a (4-fluorophenylmercapto)methyl group with 4-fluorothiophenol (96MIP4); to an azidomethyl group with  $\text{NaN}_3$  heated in DMF (90MIP1; 92MIP1, 92MIP6, 92MIP8); and to a 2,2-di(methoxycarbonyl)ethyl group with sodio malonate (92MIP6, 92MIP8); and it reacted with 3,3-pentamethylene, and tetramethyleneglutarimide, succinimide, phthalimide, and other similar substituted derivatives and heterocyclic analogs; with pyrazole, 1,2,4-triazole and tetrazole in the presence of NaH (90MIP1; 92MIP1, 92MIP6, 92MIP8; 96MIP3); and with 4-(*p*-fluorobenzoyl)piperidine (92MIP6, 92MIP8). A 7- and 8-[2,2-di(methoxycarbonyl)ethyl] group in a perhydropyrido[1,2-*a*]pyrazine skeleton was hydrolyzed and decarboxylated, and a 7-(2-carboxyethyl) group was esterified with MeOH and was reduced with LAH to give the respective 7- and 8-(3-hydroxypropyl) derivatives (92MIP6, 92MIP8). The 7- and 8-(3-hydroxypropyl) groups were acylated with  $\text{MeSO}_2\text{Cl}$  (92MIP8). The hydroxy group of 2-(2-hydroxyethyl and 3-hydroxypropyl)perhydropyridol[1,2-*a*]pyrazines was converted into a chlorine atom with  $\text{SOCl}_2$  (71GEP2029185, 71JPP71/34717; 72FRP2092785, 72GEP2226063). A 3-hydroxymethyl group was acylated with PhNCO (59CB240). Hydrog-

enation of 7-hydroxymethyl-2-{3-[5-dibenz(*b,f*)azepin-5-yl]}propyl}perhydropyrido[1,2-*a*]pyrazine over 10% Pd-C in EtOAc gave 2-{3-[10,11-dihydrodibenz(*b,f*)-azepin-5-yl]}propyl} derivatives (96MIP3).

Reduction of 2-nitroso-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one with Zn in H<sub>2</sub>SO<sub>4</sub> gave the 2-amino derivative (87MI6). The amino group was reacted with (het)aroyl chlorides and aldehydes (87MI6). 2-Aminoperhydropyrido[1,2-*a*]pyrazine was obtained from its 2-nitroso derivative with LAH (85EUP135837, 85USP4551450). Catalytic hydrogenation of 2-benzoyl-, and 2-(1- and 3-cyclohexenylcarbonyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones over PtO<sub>2</sub> or Pd-C gave the 2-cyclohexylcarbonyl derivative (76GEP2457971; 81GEP3011156; 84GEP3316928).

The amino group of 2-(4-aminobenzoyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one, obtained by catalytic hydrogenation of its 4-nitro derivative over Pd-C, was acetylated and methylated (76GEP2457971; 84GEP3316928). A 4-dimethylamino derivative reacted with MeI (76GEP2457971). Catalytic reduction of a 2-(4-oximinocyclohexylcarbonyl) derivative, prepared from a 2-(4-oxocyclohexylcarbonyl) derivative and HONH<sub>2</sub> over Raney Ni, gave a 2-(4-aminocyclohexylcarbonyl) derivative (76GEP2457971; 84GEP3316928).

*N*-Alkyl derivatives were obtained on the reduction with LAH of 3-acyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines (67SAP67/05764, 67SAP67/05767; 69GEP1901262, 69IJC833; 70JMC516, 70SWP498849), and 2-acyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines (65BEP 659249). Catalytic hydrogenation of 2-propargyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazinol[2,1-*a*]isoquinoline gave the 2-propyl derivative. Reduction of 2-[3-(4-methylpiperazino)-1,3-dioxopropyl], and 2-aminocarbonylmethyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline with LAH afforded the 2-[3-(4-methylpiperazino)propyl], and 2-(2-aminoethyl) derivatives. An amino group reacted with H<sub>2</sub>NCN, with MeCN in the presence of AlCl<sub>3</sub> and with CH<sub>2</sub>O-HCO<sub>2</sub>H to give 2-[2-guanidino, 2-(acetamidino), and 2-dimethylaminoethyl] derivatives, respectively (65BEP659249).

Condensation of 7-formylperhydropyrido[1,2-*a*]pyrazine with nitromethane in the presence of Na<sub>2</sub>CO<sub>3</sub> in MeOH afforded the 7-(2-nitro-1-hydroxyethyl) derivative, which was dehydrated to the 2-nitrovinyl derivative on treatment with Ac<sub>2</sub>O (93MIP7; 95TA321). Treatment of 8-methoxy-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline with boiling 48% HBr in the presence of a small amount of H<sub>3</sub>PO<sub>2</sub> gave the 8-hydroxy derivative (67SAP67/05768).

Reactions of 2,3-dioxo-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-5-carboxylic acids and the homologous acetic and propionic acids, prepared by basic hydrolysis of the corresponding ester, with amines, 28%

NH<sub>4</sub>OH, and hydroxylamine derivatives in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide and hydroxybenztriazole in DMF (93MIP2; 94JMC3956; 95BMC1527, 95BMC1533), in the presence of NEt<sub>3</sub> and *N,N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride in CH<sub>2</sub>Cl<sub>2</sub> (93MIP2; 94CP2121609, 94EUP627434; 95BMC1527) or in the presence of NEt<sub>3</sub> and isobutyl chloroformate at -20°C in DMF (93MIP2), gave the appropriate carboxamide derivative. Under similar conditions 10-bromo-5-aminomethyl-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,3-dione, obtained from its 5-(phthalimidomethyl) derivative by acidic hydrolysis, was acylated with PhCNO, ethyl chlorooxalate, and benzoic acid in the presence of NEt<sub>3</sub>, 1-ethyl-3-[(3-dimethylamino)propyl]carbodiimide and *N*-hydroxybenzotriazole (93MIP2; 94JMC3956). Side-chain *tert*-butoxycarbonylamino, 2,3-di-*tert*-butoxycarbonylguanidino, *tert*-butoxycarbonylmethoxy, ethoxalylaminomethyl, and *O*-tetrahydropyranyl-*N*-hydroxycarbamoylmethyl groups in 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,3-dione skeletons were converted into amino, guanidino, carboxymethoxy, oxaloaminomethyl, and *N*-hydroxycarbamoylmethyl groups by hydrolysis, and an *o*-aminophenylcarbamoylmethyl group was converted into a 2-benzimidazolylmethyl group in a 5 : 1 mixture of MeCN and conc. HCl at 50°C (93MIP2; 94CP2121609, 94EUP627434). A side-chain benzyloxycarbonylamino group in 7-oxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylic acid was deprotected by hydrogenation over Pd-C (94CPB2569). Side-chain ester and acetoxy groups were hydrolized, a side-chain carboxylic group was esterified, and a side-chain amino group reacted with di-*tert*-butyl dicarbonate. Side-chain 3,3-dicarboxypropyl groups were decarboxylated to give 3-carboxypropyl derivatives (94CP2121609, 94EUP627434). 5-Hydroxymethyl derivatives were obtained from 9-bromo-2,3-dioxo-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-5-carboxylic acids by treatment with NEt<sub>3</sub> and isobutyl chloroformate at -15°C in DMF, then *N*-hydroxysuccinimide and dimethylaminopyridine, followed by reduction of the activated ester with NaBH<sub>4</sub> in THF (93MIP2). A 5-hydroxymethyl group was acylated with MeSO<sub>2</sub>Cl, and a 5-methylsulfonyloxymethyl group was converted into an iodomethyl group on heating with NaI in DMF at 60°C. An iodomethyl group gave a cyanomethyl group with NaCN, and a hydroxymethyl group was oxidized into a formyl group by Dess-Martin periodinane. A benzylaminomethyl group was obtained when a formyl group was reacted with benzylamine and the resultant Schiff base was reduced with NaBH<sub>4</sub> (93MIP2).

The hydroxy group of 2-(2-hydroxyethyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline reacted with acyl chlorides and propargyl bromide (65BEP659249). Hydroxy groups of 2-benzoyl-9,10-dihydroxy-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one, obtained from

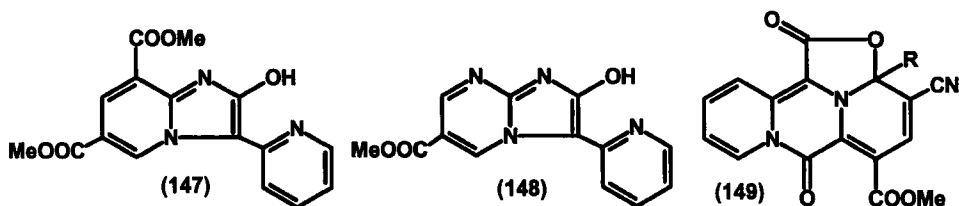


9,10-dimethoxy or 9,10-dibenzyloxy derivatives by treatment with  $\text{BBr}_3$  or by hydrolysis, respectively, were methylated with diazomethane (76GEP2441261).

The oxidation of 2-cyclohexylcarbonyl-2,3,6,7-tetrahydro- and 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones with *m*-CPBA gave a ring-opened product, and the 2-(3-pyridylcarbonyl)hexahydro derivative afforded the pyridine-*N*-oxide derivative [89AP(322)795]. Oxidation of 2-(2-pyridylcarbonyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one with *m*-CPBA gave the 1-hydroxy derivative (76GEP2441261). A microbiological oxidation of 9-chloro-8-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline yielded the 8-hydroxy-methyl derivative (69GEP1901262). Pyrolysis of *N',N'',N'''*-triethyl-6-ethylimino-2-methyl-1-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrazine-7,8,9-tricarboxamide *in vacuo* at 150–160°C gave a pyrrolo[3',4':3,4]pyrido[1,2-*a*]pyrazine derivative (74HCA750).

## 6. Ring Transformations

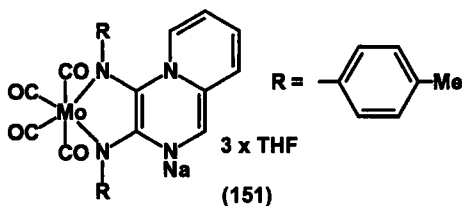
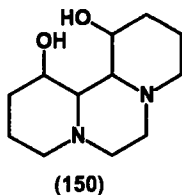
Heating either trimethyl 2-methyl-6-ethylidene-2,6-dihydro-1*H*-pyrido[1,2-*a*]pyrazine-7,8,9-tricarboxylate or tetramethyl 1,2-dimethyl-2,9*a*-dihydro-1*H*-pyrido-[1,2-*a*]pyrazine-6,7,8,9-tetracarboxylate in dilute HCl gave dimethyl 2-methyl-7-propionyl-1,6-dioxo-2,6-dihydro-1*H*-pyrido[1,2-*a*]pyrazine-8,9-dicarboxylates (62JCS1510). 1,12-Dihydroxyperhydrodibenzo[*ac*]pyrazine was prepared from 1-(2-tetrahydrofuryl)-9-hydroxyperhydropyrido[1,2-*a*]pyrazine in  $\text{Ac}_2\text{O}$  saturated with HBr at 95–100°C (61BSF2135).



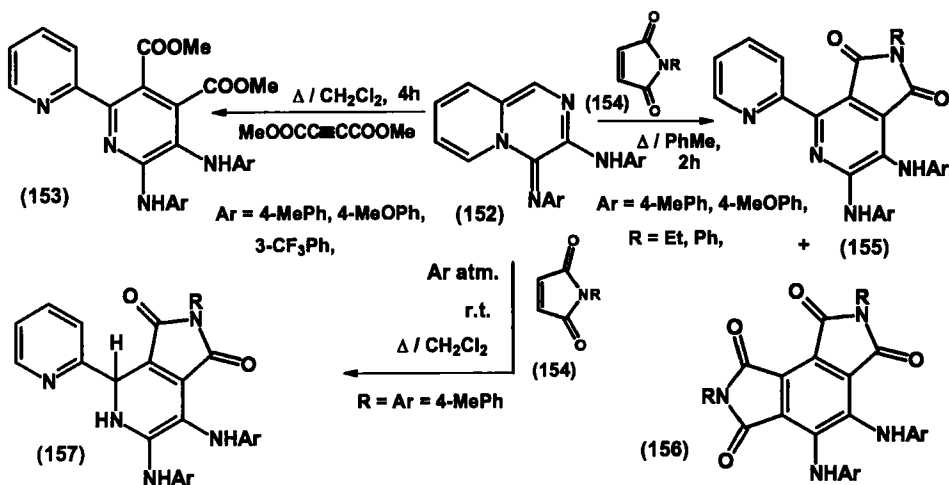
Reaction of pyrido[1,2-*a*]pyrazin-4-one **145** with methyl cyanoacetate, cyanamide, and  $\beta$ -oxo nitriles in AcOH at 70°C gave imidazo[1,2-*a*]pyridine **147**, imidazo[1,2-*a*]pyrimidine **148**, and tetracyclic heterocycles **149**, respectively (96JHC639).

Stevens rearrangement of methiodides of 2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinolin-1-ones in the presence of 0.5 eq LAH gave 1'-methylindane-2-spiro-2'-piperazin-3'-ones (73CPB2661). When 10 eq LAH were applied, the oxo group of the spiro derivatives was also reduced [74GEP2356999, 74JAP(K)74/72276].

Treatment of 1-(2-tetrahydrofuryl)-9-hydroxyperhydropyrido[1,2-*a*]-pyrazine with HBr gave dipyrido[1,2-*a*;2',1-*c*]pyrazine **150** (58FRP 1167644). Treatment of 3-(*p*-methylphenylamino)-4-(*p*-methylphenylimino)-4*H*-pyrido[1,2-*a*]pyrazine with 30% H<sub>2</sub>O<sub>2</sub> in acetone at 50°C gave 1-(*p*-methylphenyl)-2-(2-pyridyl)-4-(*p*-methylphenylamino)-1,2-dihydro-5*H*-imidazol-5-one, and with sodium bis(trimethylsilyl)amide and (norbornadiene)Mo(Co)<sub>4</sub> in THF it afforded complex **151** [95JPR(337)38].



Reaction of 3-amino-4-imino-4*H*-pyrido[1,2-*a*]pyrazines **152** with DMAD and maleimides **154** yielded 2,2'-bipyridine-3,4-dicarboxylates **153**, and mixtures of bi- and tricyclic derivatives **155** and **156**, respectively [96JPR(338)430]. In the cases of maleimide reactions, higher temperature (at 160°C in xylene) in an autoclave gave only **156**. When pyrido[1,2-*a*]pyrazine **152** (Ar = 4-MePh) was reacted with *N*-(4-methylphenyl)-maleimide in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature, **157** could be isolated.



## 7. Miscellaneous

Racemic *trans*-7,9*a*-H-7-hydroxymethyl-2-(2-pyrimidinyl)perhydropyrdo[1,2-*a*]pyrazine was resolved into its enantiomers by diastereomeric salt

formation with L-(+)- and D-(-)-tartaric acids (92MIP5). Racemic *cis*-7,9a-H-7-aminomethyl-2-(2-pyrimidinyl)perhydropyrido[1,2-*a*]pyrazine was resolved into its enantiomers by diastereomeric salt formation with (-)-mandelic acid (90MIP1; 92MIP1). Racemic 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one was resolved with quinic acid (75GEP2331713) and with enantiomers of tartaric acid (65BEP659249). Racemic *cis*-2-methyl-7-phenyl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline was resolved into its enantiomers by diastereomeric salt formation with (+)- or (-)-dibenzoyltartaric acid (84EUP107825, 84JMC995). Racemic *cis*- and *trans*-7,9a-H-2-(3-benzisoxazolyl)-7-hydroxymethyl and -7-(2-aminoethyl)perhydropyrido[1,2-*a*]pyrazines and an *N*-BOC derivative were resolved into enantiomers by crystallization of the D-(-)-tartrate and (S)-(+)- and (R)-(-)-mandelate salts (92MIP8; 93MIP1, 93MIP7; 95TA321). A 1 : 4.5 mixture of the *cis* and *trans* epimers of 7-(4-chlorophenyl)-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-1-one was isomerized into a 1 : 99 mixture of the *cis* and *trans* epimers in the presence of a catalytic amount of NaOMe in MeOH [89H(29)359, 89JAP(K)89/31772]. A 15 : 1 mixture of *trans*- and *cis*-7,9a-H-2-(3-benzisoxazolyl)-7-formylperhydropyrido[1,2-*a*]pyrazines was obtained when the *cis* isomer was treated with a catalytic amount of Na<sub>2</sub>CO<sub>3</sub> in MeOH for 18 h (93MIP7; 95TA321). A study has been made of the base-catalyzed racemization of 2-methylperhydropyrido[1,2-*a*]pyrazine-1,4-diones (e.g., **48**, R = Me) derived from optically active pipercolic acid (81TL3101). A pyrido[1,2-*a*]pyrazine salt of *N*-methyl-*N*-(phenylaminothiocarbonyl)-2-carboxybenzoic hydrazide was formed (80EUP9324; 81USP4282031).

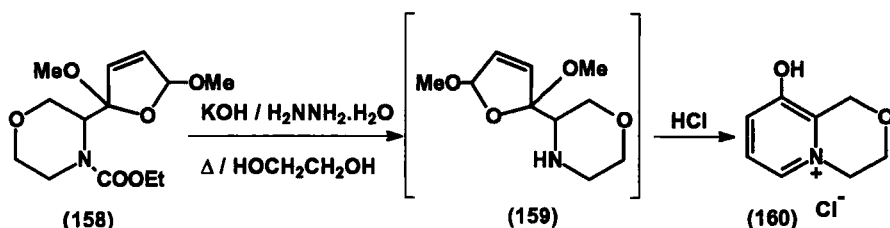
## IV. Synthesis

### A. PYRIDO[2,1-*c*][1,4]OXAZINES AND THEIR BENZO DERIVATIVES

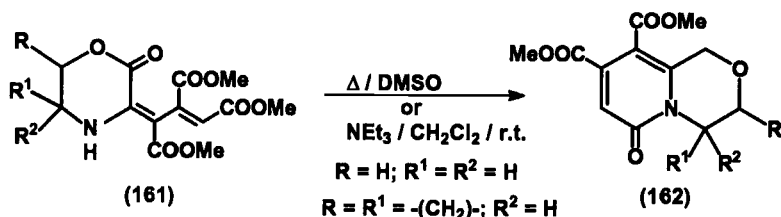
#### 1. *By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom* [6 + 0( $\alpha$ )]

Distillation of 2-piperidylmethyl ethoxycarbonylmethyl ether *in vacuo* gave perhydropyrido[2,1-*c*][1,4]oxazin-4-one (57N584). This bicycle was also obtained from 2-pyridylmethyl 2-ethoxycarbonylmethyl ether by hydrogenation over PtO<sub>2</sub> in AcOH [60AP(293)74]. Heating (2-piperidyl)[(o-ethoxyphenyloxy)methyl]methyl ethoxycarbonyl ether in toluene afforded 1-[(o-ethoxyphenyloxy)methyl]perhydropyrido[2,1-*c*][1,4]oxazin-4-one (88EUP279707). Cyclization of 1-carboxypentyl pipercolinate with bis(2-oxo-3-oxazolidinyl)phosphinic chloride in DMF at 0°C in the presence of NEt(*i*-Pr)<sub>2</sub> afforded 3-butylperhydropyrido[2,1-*c*][1,4]oxazine-1,4-dione

(96GEP4440193). Perhydropyrido[2,1-*c*]oxazine and its 4-phenyl derivative were prepared from 2-piperidylmethyl 2-bromoethyl and 2-bromo-2-phenylethyl ethers on treatment with NaOEt [58N516; 60AP(293)74; 63AP(296)38], or from 2-pyridylmethyl 2-hydroxyethyl ether by hydrogenation over Raney Ni at 210–215°C under 120 atm [58N516; 60AP(293)74]. Cyclization of 2-piperidylmethyl allyl ether occurred on the action of Hg(OAc)<sub>2</sub> and subsequent treatment with NaBH<sub>4</sub>, to give 4-methylperhydropyrido[2,1-*c*][1,4]oxazine (72TL4013).

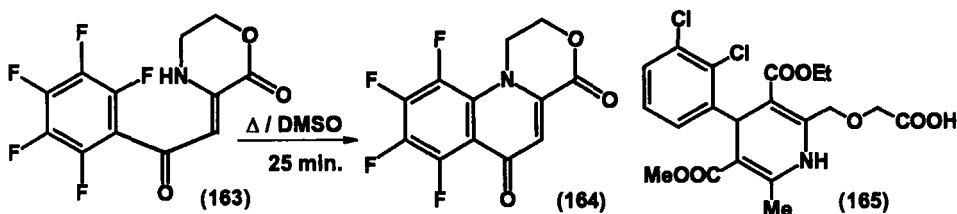


Morpholine **158** was refluxed in ethylene glycol containing KOH and H<sub>2</sub>NNH<sub>2</sub> H<sub>2</sub>O, the cooled mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the resulting crude **159** was heated with 1 N HCl to give 1*H*-pyrido[2,1-*b*]-[1,4]oxazinium chloride (**160**) (83CL21).



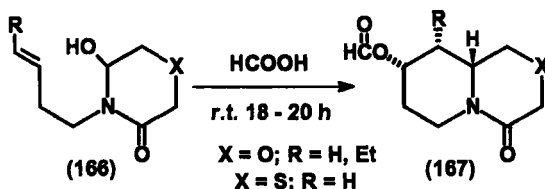
Heating tricarboxylate **161** in DMSO [84H(22)1729; 87CPB457] or its treatment with NEt<sub>3</sub> (89JHC847) gave 1,6-dioxopyrido[2,1-*c*][1,4]oxazine-8,9-dicarboxylate (**162**). In similar reactions derivatives of the 5,6-benzologue of **161** gave complex reaction mixtures, from which derivatives of the 3,4-benzologue of pyrido[2,1-*c*][1,4]oxazine-8,9-dicarboxylate (**162**) and sometimes 8-carboxylates could be isolated [85H(23)2401; 87CPB457; 89JHC847].

Cyclization of methyl 4-(*cis*-3,5-H-2-oxomorpholin-5-yl)butyrate in boiling toluene provided *cis*-4,9*a*-H-4-phenylperhydropyrido[2,1-*c*][1,4]oxazine-3,6-dione [95H(41)1931]. Heating 1,4-oxazin-2-one **163** afforded [1,4]oxazino[4,3-*a*]quinoline-4,6-dione **164** (94IZV299, 94JFC119). The reaction of carboxylic acid **165** with 1,1'-carbonyldiimidazole in the presence of 4-methylmorpholine afforded pyrido[2,1-*c*][1,4]oxazin-4-one (**61**)



(85EUP161917, 85EUP164247; 91JMC19). 1,3,4,6,7,11*b*-Hexahydro[1,4]oxazino[3,4-*a*]isoquinoline and its 4-oxo derivative were obtained by cyclization of 3-[*o*-(2-chloroethyl)phenyl]morpholine and 1-[(2-chloroethoxy)-methyl]-1,2,3,4-tetrahydroisoquinoline on the action of *tert*-BuOK, and by cyclization of 2-[*o*-(3-morpholinyl)phenyl]acetyl chloride on the action of NEt<sub>3</sub> (67BRP1094470, 67NEP6611733).

Treatment of 8-allyloxyquinolines with halogens gave 3-halomethyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzoxazinium halides (93MI4). Thermal cyclization of 8-(2-chloroethoxy)quinolines and 8-quinolyl 2-bromoacetate and its 2-substituted derivatives furnished 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]benzoxazinium chlorides [94KFZ(12)50; 95KFZ(5)48] and 2-oxo-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzoxazinium bromides (65 UKZ1182; 66URP178820), respectively. Heating 8-(2-chloroethoxy)-1,2,3,4-tetrahydroquinoline at 130°C and 4-hydroxy-8-[(ethoxycarbonylmethyl)oxy]quinoline at 170°C led to 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine (44HCA1756) and 2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-dione [70CR(C)1189], respectively. Cyclization of 1-(chloroacetyl)-8-hydroxy-1,2,3,4-tetrahydroquinolines with NEt<sub>3</sub> gave 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]benzoxazin-3-one [69CR(C)564]. Cyclization of 8-(3-chloro-2-hydroxypropoxy)quinolin-2(1*H*)-ones in EtOH on the action of NaOH gave 3-hydroxymethyl-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-ones (79 GEP2854727).

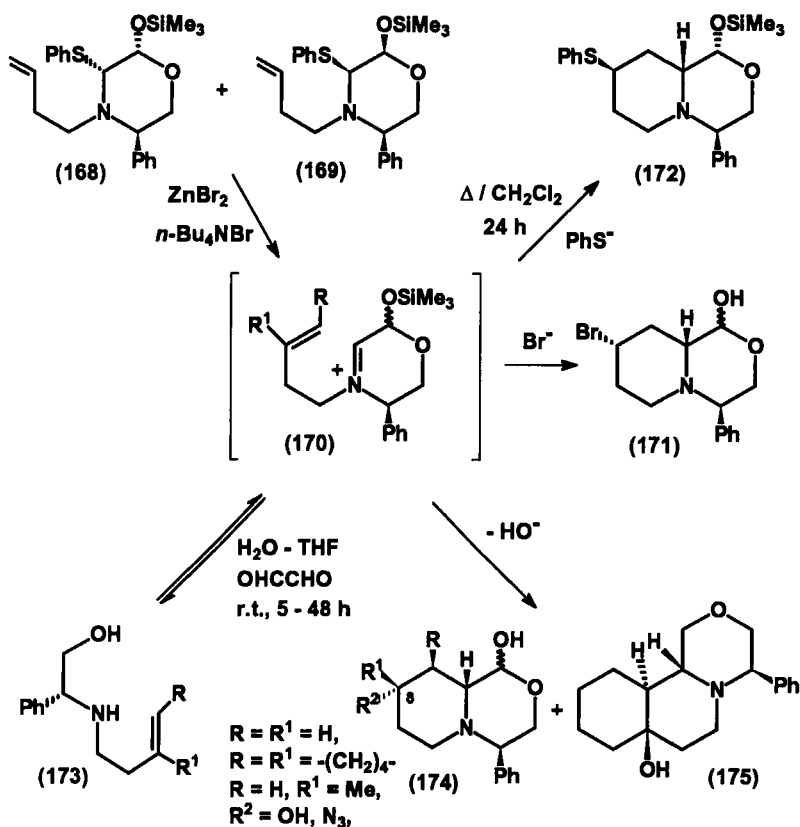


## 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6 + 0( $\beta$ )]

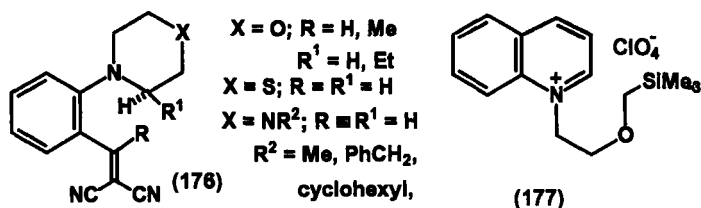
The formic acid-mediated biomimetic  $\alpha$ -acylimminium ion cyclization of 4-alkenyl-5-hydroxymorpholin-3-ones (166, X = O) yielded equatorial for-

mates **167**, ( $X = O$ ) with a *trans* ring junction in a highly stereospecific manner (81EUP34015; 83TL91; 85T2007). A nucleophile-mediated cyclization of epimeric oxazines **168** and **169** via ene-iminium ions **170** resulted stereoselectively in a mixture of epimers **171** (Scheme 9) (90SL731; 92T431). When the cyclizations of **168** and **169** were carried out in the presence of  $ZnCl_2$  and thiophenol, epimeric 8-phenylthio derivatives **172** were obtained (92T431). In similar reactions, epimeric pyrido[2,1-*c*][1,4]oxazines **174** ( $R = R^1 = Me$ ) and [1,4]oxazino[3,4-*a*]isoquinolines **175** were obtained from  $\beta$ -amino alcohols **173** with glyoxal (92T431). When  $NaN_3$  was also present in the aqueous reaction mixture, a 1 : 5 mixture of **174** ( $R^1 = Me$ ,  $R^2 = OH$ ) and its 8-azido derivative **174** ( $R^1 = Me$ ,  $R^2 = N_3$ ) was produced.

Heating dinitriles **176** ( $X = O$ ) gave hexahydro[1,4]oxazino[4,3-*a*]quinolines **107** ( $X = O$ ) (84JOC269; 89JOC209). Irradiation of the quinolinium perchlorate **177** in MeCN, followed by catalytic hydrogenation over  $PtO_2$ , yielded 1,2,4,4*a*,5,6-hexahydro[1,4]oxazino[4,3-*a*]quinoline (84JA6855).

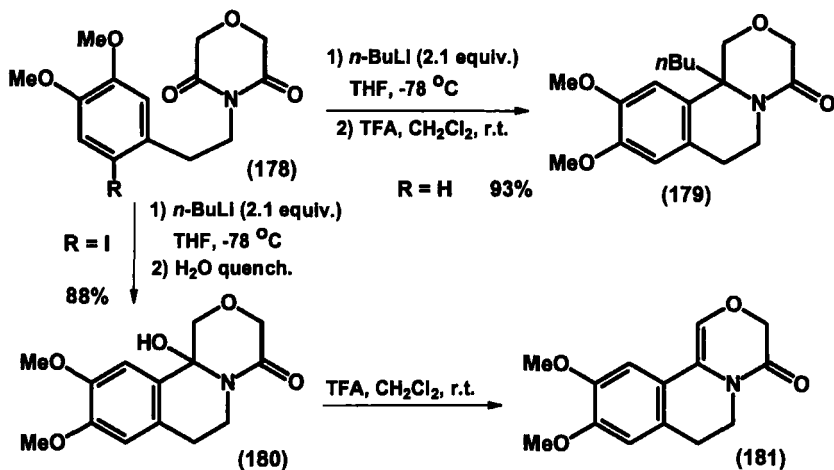


SCHEME 9

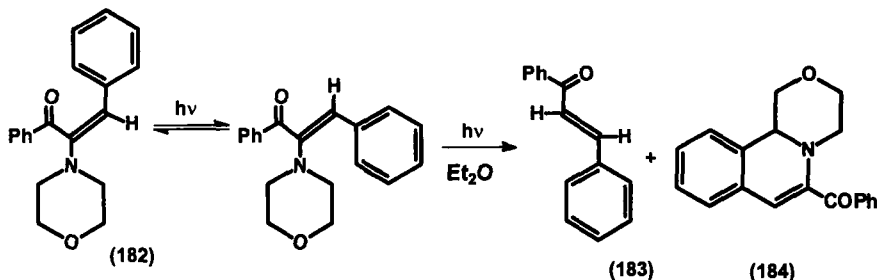


Cyclization of 2-carbamoyl-4-(3,4-dimethoxyphenethyl)morpholin-5-one in boiling 0.6 N alcoholic KOH afforded 9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline-2-carboxamide (68SAP68/02790). 1,3,4,6,7,11*b*-Hexahydro[1,4]oxazino[3,4-*a*]isoquinolines were obtained when the products of the Bischler-Napieralski cyclization of 4-(2-arylethyl)-morpholin-3-ones with  $POCl_3$  (67BRP1094470, 67NEP6611733; 68SAP68/02790; 78JMC785; 85AJC1591) were reduced with  $NaBH_4$ , or over Pd-C with  $H_2$  (78JMC785). Reduction with  $NaBD_4$  gave the 11*b*-deutero derivative (78JMC785). When the starting morpholinone contained a carboxamide group in position 6, a *cis-trans* mixture of 3-cyano derivatives of the tricycle was obtained (68SAP68/02790; 78JMC785).

1,4-Oxazino[3,4-*a*]isoquinolin-4-ones **179–181** were obtained from 4-[2-(3,4-dimethoxyphenyl)ethyl]-1,4-oxazine-3,5-dione (**178**) as depicted in Scheme 10 (96TL6193). Irradiation of the *E*-isomer of  $\alpha$ -morpholinochalcone (**182**) resulted in the formation of a mixture of chalcones (**183**) and 1,3,4,11*b*-tetrahydro[1,4]oxazino[3,4-*a*]isoquinoline (**184**) (79T2501).



SCHEME 10



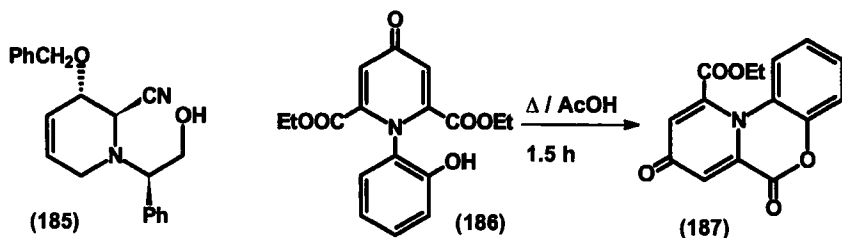
### 3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )]

1-(2-Hydroxyethyl)-2-hydroxymethylpiperidines and their 5,6-benzo derivatives (72IJC1134) were heated in conc. HBr (61JMC187; 721JC1134; 76JMC334; 78JMC460), in diluted or conc.  $H_2SO_4$  [58N516; 60AP(293)74; 78JMC460; 92CPB652], or in  $Ac_2O$  (61JMC187) to afford perhydropyrido[2,1-*c*][1,4]oxazines and 1,2,4,4a,5,6-hexahydro[1,4]oxazino[4,3-*a*]-quinolines.

Dimethyl 6-methyl-3-oxo-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazine-7,9-dicarboxylate was prepared from methyl 2-[2-(bromomethyl)-6-methyl-3,5-bis(methoxycarbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridin-1-yl]acetate in boiling 80% aqueous MeOH in the presence of  $K_2CO_3$ , and from 2-[2-(hydroxymethyl)-6-methyl-3,5-bis(methoxycarbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridin-1-yl]acetic acid in boiling  $Ac_2O$  for 1 day (95PHA681). Ring closure of 2-[phenyl(hydroxy)methyl]-1-(ethoxycarbonylmethyl)pyridinium bromide in AcOH in the presence of 48% HBr gave 1-phenyl-3-oxo-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]oxazin-9-one bromides (64CB3566). 2-Ethoxycarbonyl-1-(phenyl- or methylcarbonylmethyl)pyridinium bromides and 1-ethoxycarbonyl-2-(phenylcarbonylmethyl)isoquinoline in a mixture of conc. HBr and  $Ac_2O$  yielded 3-substituted 1-oxo-1*H*-pyrido[2,1-*c*][1,4]oxazin-9-one bromides and 1-oxo-3-phenyl-1*H*-[1,4]oxazino[3,4-*a*]isoquinolin-9-one bromide, respectively (64CB3566).

Treatment of ethyl 1-[2-[(*tert*-butyl, dimethylsilyl)oxy]-1-phenylethyl]-6-alkylpiperidine-2-carboxylates with 10% HF in MeCN afforded diastereomeric mixtures of 4-phenyl-6-substituted perhydropyrido[2,1-*c*][1,4]oxazin-1-ones (94JOC3769). Dieckmann cyclization of ethyl 4-(3-ethoxycarbonylpropyl)morpholine-3-carboxylate with *tert*-BuOK in  $Et_2O$  and subsequent ester hydrolysis and decarboxylation furnished perhydropyrido[2,1-*c*][1,4]oxazin-9-one (82EUP57536; 92BMC1293). Mild acidic hydrolysis of the nitrile moiety of amino nitrile **185** gave pyrido[2,1-*c*][1,4]oxazin-1-one **60** (96TL4001).

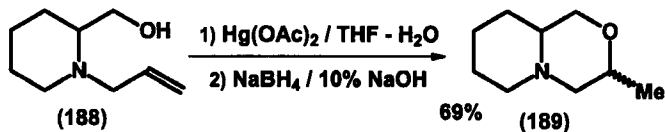




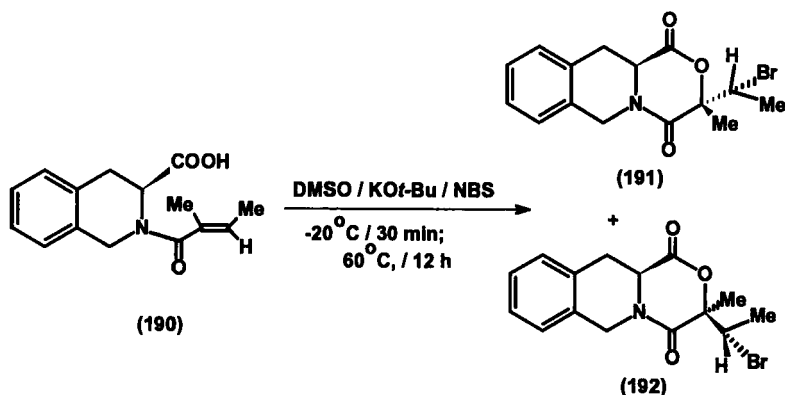
Heating *N*-(*o*-hydroxyphenyl)-4-piperidone **186** in boiling AcOH gave pyrido[2,1-*c*][1,4]oxazine-10-carboxylate (**187**) [85IJC(B)182].

Cyclization of 3-phenyl-4-(chlorocarbonylmethyl)morpholine in the presence of  $\text{AlCl}_3$  yielded 1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinolin-7-one (67BRP1094470, 67NEP6611733). Treatment of 1-hydroxymethyl-2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinoline with *tert*-BuOK at room temperature overnight gave 1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinolin-4-one (67BRP1094470, 67NEP6611733). 1,3,4,6,7,11*b*-Hexahydro[1,4]oxazino[3,4-*a*]isoquinolines were prepared from 1-hydroxymethyl-2-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolines in boiling 48% aqueous HBr, from 1-hydroxymethyl-2-(2-chloroethyl)-1,2,3,4-tetrahydroisoquinoline with *tert*-BuOK, and from 3-phenyl-4-(2-bromoethyl)morpholine with  $\text{AlCl}_3$  in  $\text{PhNO}_2$  (67BRP1094470, 67NEP6611733). 9,10-Dimethoxy-1,3,4,6,7,11*b*-hexahydro[1,4]oxazino[3,4-*a*]isoquinolin-3-one was obtained when 1-hydroxymethyl-2-cyanomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was heated in EtOH containing HCl [66 AP(299)997].

1,2,4,4*a*,5,6-Hexahydro[1,4]oxazino[4,3-*a*]quinolin-1-one was prepared by the cyclization of 2-(chloromethylcarbonyloxymethyl)-1-chloroacetyl-1,2,3,4-tetrahydroquinoline by treatment with *tert*-BuOK (72IJC1134).

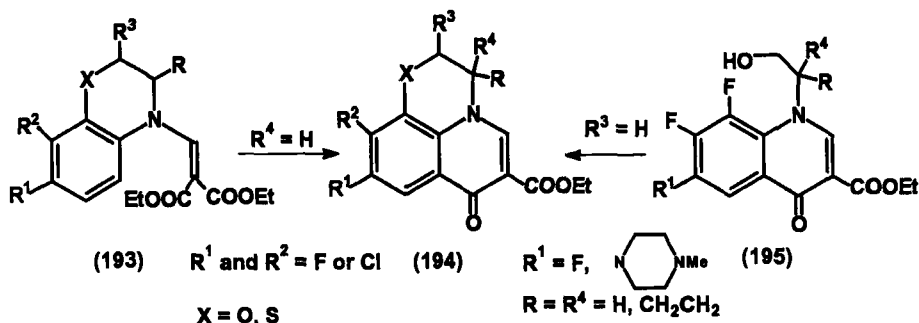


Epimers of 3-methylperhydropyrido[2,1-*c*][1,4]oxazine (**189**) were prepared by oxymercuration-demercuration of 1-(3-propenyl)-2-hydroxymethylpiperidine (**188**) [93JCR(M)1620, 93JCR(S)251]. Asymmetric bromolactonization of optically active tetrahydroisoquinoline-3-carboxylic acid **190** gave a 5 : 1 mixture of 1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinoline-1,4-diones (**191**) and (**192**) (77CL1109; 79T2345).



When 1-(2-chloroethyl)-1,2,3,4-tetrahydroquinolin-8-ols were treated with NaOH in 80% aqueous MeOH, 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines were obtained (44HCA1756; 82S692). Cyclization of 1-(2-haloacyl)-8-hydroxy-1,2,3,4-tetrahydroquinolines with alkaline hydroxide afforded 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-ones [92PIA(A)549]. Cyclization of 1-(3-chloropropionyl)- and 1-acroyl-1,2,3,4-tetrahydroquinolin-8-ols with 50% NaH in boiling DMF gave a mixture of 2,3,4,6,7,8-hexahydropyrido[1,2,3-*ef*]-1,5-benzoxazepin-4-one and 2-methyl-2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one [92PIA(A)549]. A longer reaction time was favorable to the formation of the latter. Similarly, 1-cinnamoyl and 1-( $\alpha$ -methylcinnamoyl)-1,2,3,4-tetrahydroquinolin-8-ols gave 2-benzyl and 2-benzyl-2-methyl derivatives of 2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one [92PIA(A)549]. (*Z*)-2-Benzylidene-2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one was prepared by cyclization of both 1-(2,3-dibromo-3-phenylpropionyl) and 1-PhC $\equiv$ CCO derivatives of 1,2,3,4-tetrahydroquinolin-8-ole [92PIA(A)549]. Cyclization of 1-(dichloroacetyl)-1,2,3,4-tetrahydroquinolin-8-ole in the presence of primary and secondary amines or in warm aqueous 5% NaOH yielded 2-amino-2,3,5,6-tetrahydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-ones and the 2-[(1,2,3,4-tetrahydro-8-quinolinyl)oxy] derivative, respectively [92PIA(A)549]. Cyclization of 3-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)propionic acids in polyphosphoric acid (PPA) at 120°C gave 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3,7-diones [69CR(C)564; 70CR(C)498; 72AJC1283].

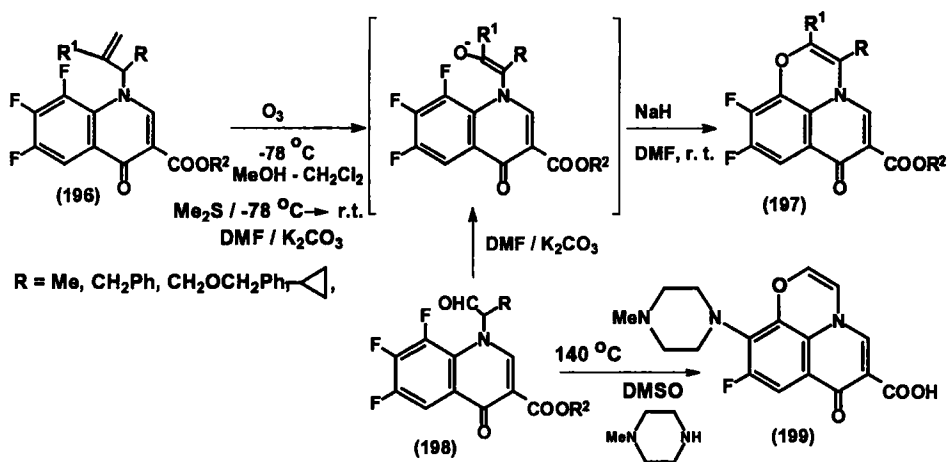
7-Oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates or 6-carboxylic acids (**194**, X = O) were prepared by the cyclization of (3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)methylenemalonates (**193**, X = O) on heating in Ph<sub>2</sub>O [86JAP(K)86/204188], in PPA (75USP3883522; 76USP3984548; 84USP4443447; 89MI5) at 120–150°C, in ethyl polyphos-



phate (PPE) [83JAP(K)83/52290, 83JAP(K)83/72588; 84CPB4907, 84EUP101829; 86EUP184384; 90EUP368410; 93MIP1078236] at 120–145°C, in boiling  $CHCl_3$  with trimethylsilyl superpolyphosphate (90EUP 376870), or by treatment with a mixture of  $Ac_2O$  and conc.  $H_2SO_4$  [84JAP(K)84/122493; 86EUP206283; 87ABC1265; 88EUP273399; 94MIP3] or with  $AcCl$  in conc.  $H_2SO_4$  [84JAP(K)84/216890]. When the cyclization was carried out in the presence of  $BF_3$ –THF in Dowtherm [83JAP(K)83/29789] or in  $(Ac)_2O$  [85JAP(K)85/126290], or on the action of  $B(OAc)_3$  (91MI13), chelated derivatives (e.g., **90**) were obtained. Pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates (**194**,  $X = O$ ) were also obtained in the cyclocondensation of 3,4-dihydro-2*H*-1,4-benzoxazines and diethyl ethoxymethylmalonate in PPE at 130–145°C (82EUP47005; 84CPB4907). Instead of malonic acid diethyl esters (**193**,  $X = O$ ), their cyclic isopropylidene esters have also been applied. They were cyclized by heating in PPE (87JHC1509), in PPA (84EUP106489; 85EUP153163) at 65°C, or in a mixture of  $Ac_2O$  and  $H_2SO_4$  [84JAP(K)84/122493], and by treatment with  $AcCl$  in conc.  $H_2SO_4$  [84JAP(K)84/216890] to give **194** ( $X = O$ ,  $R^3 = H$ ).

7-Oxopyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates (**194**,  $X = O$ ) could be prepared from 1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylates (**195**) by treatment with a base (NaH, KOH, KF,  $K_2CO_3$  or *tert*-BuOK) [86CPB4098; 87GEP3522406, 87JAP(K)87/198685, 87JMC2283; 88JMC2004, 88USP477253; 89EUP306860, 89JAP(K)89/09992; 96MIP1; 97H(45)137]. *O*-(Dimethyl-*tert*-butylsilyl) derivatives of **195** (88TL1931) and the *O*-acetate of **195** [90MI8; 97H(45)137] have also been used. Carboxylic acid derivative **194** ( $X = O$ ,  $R = Me$ ,  $R^1 = R^2 = F$ ,  $R^3 = R^4 = R^5 = H$ ) was obtained from 1-(2-hydroxy-1-methylethyl)-6,7,8-trifluor-4-oxoquinoline-3-carboxylic acid on the action *tert*-BuOK in the presence of  $PdCl_2$  (94MIP8).

3-Substituted 7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids and esters (**197**) were prepared when 1-(1-substituted allyl)-1,4-dihy-

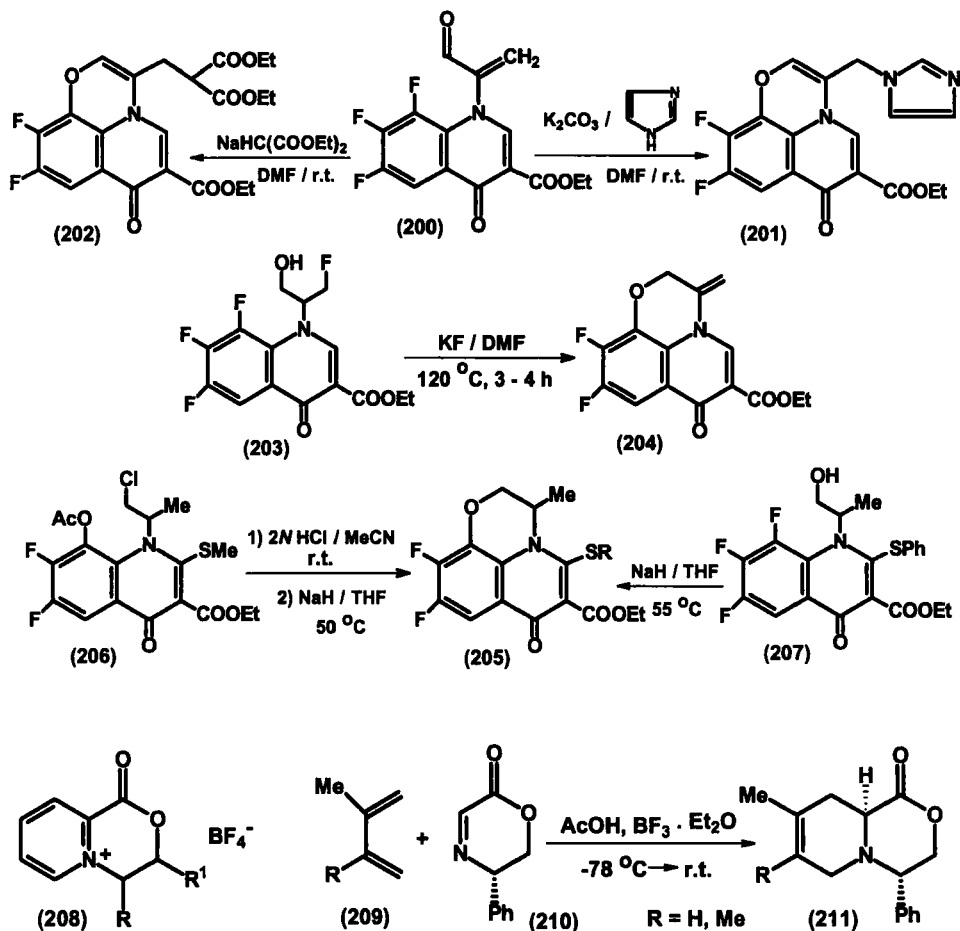


dro-4-oxoquinoline-3-carboxylic acids and esters (**196**) were treated with  $\text{O}_3$  followed by  $\text{NaH}$  (90JHC1509) or with  $\text{Me}_2\text{S}$ , then  $\text{K}_2\text{CO}_3$  in DMF (93EUP563732, 93EUP563734), or when aldehydes **198** were treated with  $\text{NaH}$  and  $\text{K}_2\text{CO}_3$  in DMF (91JHC1067) or with  $\text{NaOH}$  in aqueous  $\text{EtOH}$  (88GEP3623757; 93EUP563733). When cyclization of quinolinone **198** ( $\text{R} = \text{R}^1 = \text{H}$ ) was carried out in the presence of *N*-methylpiperazine, 10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid **199** was the product (93EUP563733). Cyclization of 1-(2-oxo-1-methyleneethyl)quinolinone **200** in the presence of imidazole or diethyl malonate and sodium gave **201** and **202** (93EUP563734). Heating the fluoro-hydrin **203** in DMF in the presence of  $\text{KF}$  afforded the 3-methylene derivative **204** (91JHC1061). 5-Methylthio and 5-phenylthio derivatives of 7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**205**) were prepared by cyclization of 4-oxo-4*H*-quinoline-3-carboxylates **206** and **207** (87EUP228661).

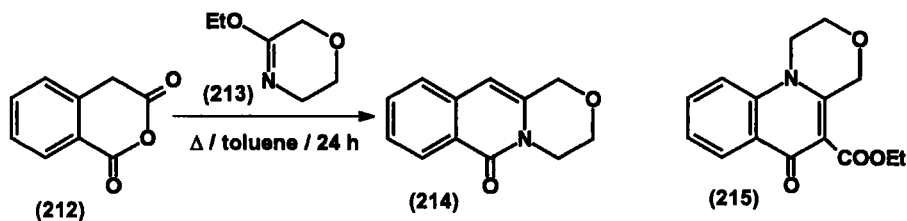
#### 4. By Formation of Two Bonds from [4 + 2] Atom Fragments

2-Ethoxycarbonyl-4,6-diphenylpyridinium tetrafluoroborate reacted smoothly with the appropriate 2-aminoethanols to give 1-oxo-3,4-dihydro-pyrido[2,1-*c*][1,4]oxazinium tetrafluoroborates (**208**) [82CS(20)147; 84JHC1609].

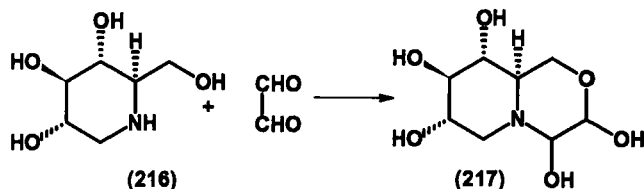
Diels-Alder reactions of (5*S*)-5-phenyl-3,4-dehydromorpholin-2-one (**210**) with isoprene and 2,3-dimethyl-1,3-butadiene (**209**) furnished (4*S*,9*aS*)-*trans*-4,9*a*-H-4-phenyl-1,3,4,6,9,9*a*-hexahydropyrido[2,1-*c*][1,4]oxazin-6-ones (**211**) (96TA2563).



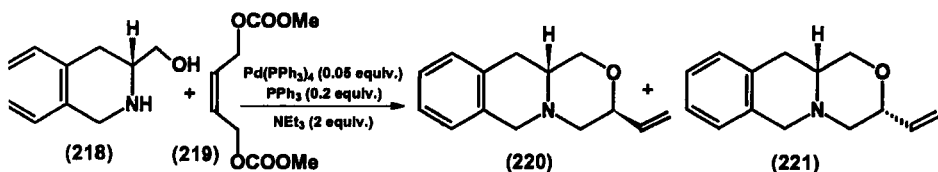
Cyclocondensation of the cyclic anhydride **212** and ethyl *o*-fluorobenzoylacetate with the imino ether **213** gave 1,3,4,6-tetrahydro[1,4]oxazino[4,3-*b*]isoquinolin-6-one (**214**) (81JHC767) and [1,4]oxazino[4,3-*a*]quinoline-5-carboxylate (**215**) (80JHC1729), respectively.



3-Oxo-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]oxazinium bromide was obtained in the reaction of 2-hydroxymethylpyridine and ethyl bromoacetate (64CB3566). The reactions of 2-hydroxymethylpiperidine and  $\alpha$ -bromoacetophenones led to 3-aryl-3-hydroxyperhydropyrido[2,1-*c*][1,4]oxazines (**25**, R = OH) [76JMC334; 78JMC460; 90AP(323)53]. When 2-hydroxymethylpiperidines and 3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline were treated with sodium in EtOH or benzene, and then with 2-chloroacetates, perhydropyrido[2,1-*c*][1,4]oxazin-4-ones [60AP(293)74; 63AP(296)38; 720MR(4)283; 90EUP350002] and 1,6,11,11*a*-tetrahydro[1,4]oxazino[4,3-*b*]isoquinolin-4(3)-one (**37**) [72OMR(4)283] were obtained, which contained a small amount of the respective 3-oxo isomers. When 2-hydroxymethylpiperidines and their 3,4- and 4,5-benzo derivatives were heated with ethyl chloroacetates, perhydropyrido[2,1-*c*][1,4]oxazin-3-ones [58N516; 60AP(293)74; 61AP(294)468; 63AP(296)38; 720MR(4)509] and their 7,8- and 8,9-benzo derivatives (**29** and **30**) were the products [720MR(4)509]. Similarly, 8-hydroxy-3-dialkylamino-1,2,3,4-tetrahydroquinoline and *cis*-4*a*,8,8*a*-H-8-hydroxyperhydroquinoline gave the respective 2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one [720MR(4)509; 90MIP3; 92JMC1076].



Cyclocondensation of 2-hydroxymethylpiperidine with 4-chloro-2-butenitrile afforded 3-cyanomethylperhydropyrido[2,1-*c*][1,4]oxazine (75-GEP2520872). The reaction of 1,5-dideoxy-1,5-diamino-D-glucitol and D-galactitol (**216**) with a 40% glyoxal solution at room temperature gave 3,4,7,8,9-pentahydroxyperhydropyrido[2,1-*c*][1,4]oxazines (**217**) (91GEP-3936295). Cyclocondensation of enantiopure 3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (**218**) and (*Z*)-1,4-bis(methoxycarbonyloxy)but-2-ene (**219**) in THF in the presence of Pd(Ph<sub>3</sub>)<sub>4</sub> (0.05 eq), PPh<sub>3</sub> (0.2 eq), and NEt<sub>3</sub> (2 eq) at 40°C gave a mixture of *cis*- and *trans*-3,11*a*-H-3-vinyl-1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinolines (**220** and **221**) (95TL5527).

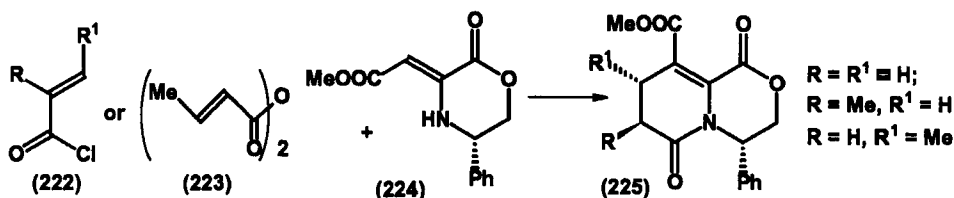


The cyclocondensation of dialkyl acetylenedicarboxylate and 1,2,3,4-tetrahydroquinolin-8-ol afforded an isomeric *E-Z* mixture of 3-alkoxy-carbonylmethylene-3,4,5,6-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-2-ones [78HCA607; 79PIA(A)1]. The reactions of 8-hydroxy-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate and 3-bromoalkynes yielded **204** and its 2-methyl derivative (91CCC1937; 92CCC216). Pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**204**) was also obtained from 8-hydroxyquinoline-3-carboxylate on treatment of DDC in pyridine with 2-propyn-1-ol at room temperature (91CCC1937). Reaction of 8-hydroxy-1,2,3,4-tetrahydroxyquinoline with oxalyl chloride in the presence of  $\text{NEt}_3$  gave 3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-2,3-dione [92PIA(A)549]. Cyclocondensation of 5-chloro-8-hydroxy-1,2,3,4-tetrahydroquinoline and chloroacetyl chloride in the presence of  $\text{K}_2\text{CO}_3$  in MeCN afforded 8-chloro-2,5,6,7-tetrahydro-3*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-one (84GEP3234529).

### 5. By Formation of Two Bonds from [3 + 3] Atom Fragments

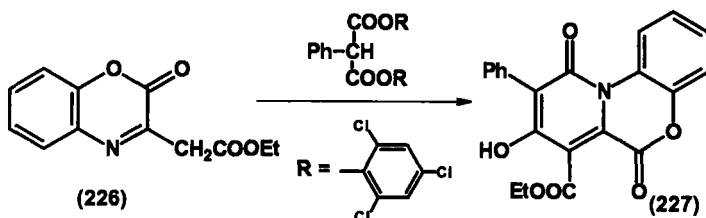
1-Oxo-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]oxazinium bromide was prepared both in the reaction of ethyl picolinate and 2-bromoethanol (64CB3566), and from picolinic acid hydrobromide and ethylene carbonate (74BCJ405). When a mixture of picolinaldehyde and 2-bromoethanol was allowed to stand at ambient temperature, 1-hydroxy-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]oxazinium bromide was obtained (78JHC347).

Heating ethyl 6-methylpicolinate and ethylene oxide in methanol in a pressure bottle afforded 6-methylperhydropyrido[2,1-*c*][1,4]oxazin-1-one (66JMC311; 68USP3388128). Similarly, 1,3,4,6-tetrahydro[1,4]oxazino[4,3-*b*]isoquinolin-1-ones were prepared in the reactions of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylates and ethylene oxide (85MI2).



Reaction of the enamino ester **224** with  $\alpha,\beta$ -unsaturated acyl chlorides **222** or anhydride **223** in boiling THF gave 4-phenyl-1,6-dioxo-1,3,4,6,7,8-hexahydropyrido-[2,1-*c*][1,4]oxazine-9-carboxylates (**225**) (95TL1657; 96JOC5736). Cyclocondensation of 2-hydroxymethyl-5-benzoyloxypyran-4-one and glycine in water gave 7-benzoyloxy-3,4,8-trihydro-1*H*-pyrido-[2,1-*c*][1,4]oxazine-3,8-dione (83AJC2307). Cyclocondensation of benzoxazineacetate **226** with bis(2,4,6-trichlorophenyl) 2-phenylmalonate gave

pyrido[2,1-*c*][1,4]benzoxazine-7-carboxylate **227** (77M103). Reaction of 3,4-dihydro-2*H*-1,4-benzoxazines and 1,3-haloalkanes yielded 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines (48USP2448869). Reaction of 3,6-dimethyl-2,3-dihydro-4*H*-benzoxazine and epichlorohydrin in 2-PrOH at 140°C under 5 atm pressure in an autoclave afforded 6-hydroxy-3,10-dimethyl-3,5,6,7-tetrahydro-2*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine (88GEP3817565; 90GEP3936250, 90GEP3940081). Cyclocondensation of ethyl 6,7,8-trifluoro-4-hydroxyquinoline-3-carboxylate with (1-chloro- and 1-bromomethyl) ketones in the presence of K<sub>2</sub>CO<sub>3</sub> in DMF at 80–90°C yielded 2-substituted 9,10-difluoro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates (**197**, R = H) (88GEP3623757; 93EUP563732–93EUP563734). Reaction of 3,4-dihydro-2*H*-1,4-benzoxazines with triethyl methanetricarboxylate at 150°C for 1 h, then at 200°C for 1 h gave ethyl 7-hydroxy-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates (93MIP4).



## 6. By Formation of Three Bonds from [4 + 1 + 1] Atom Fragments

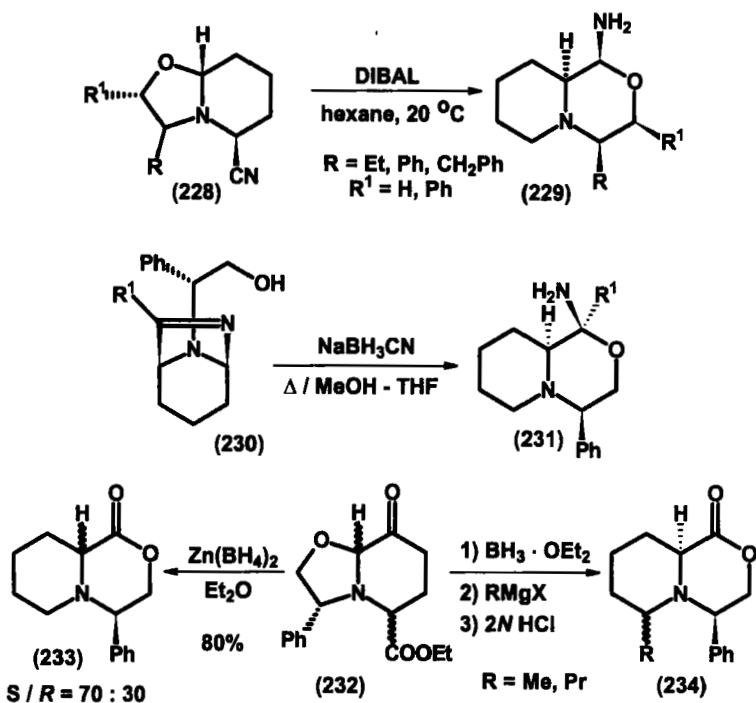
Cross double carbonylation of 2-hydroxymethylpiperidine in the presence of PdCl<sub>2</sub>(MeCN)<sub>2</sub>-CuI as catalyst under CO and O<sub>2</sub> at ambient temperature in an autoclave afforded perhydropyrido[2,1-*c*][1,4]oxazine-3,4-dione [87JAP(K)87/212377, 87JCS(CC)125].

## 7. Ring Transformations

Hydrogenation of an epimeric mixture of 5-benzoyl-3-phenylperhydrooxazolo[3,2-*a*]pyridine over PtO<sub>2</sub> gave a single isomer of 1-hydroxy-*trans*-1,4-diphenylperhydropyrido[2,1-*c*]oxazine (88SC823). Treatment of optically active 5-cyanoperhydrooxazolo[3,2-*a*]pyridines (**228**) and their enantiomers with DIBAH in hexane afforded 1-aminoperhydropyrido[2,1-*c*][1,4]oxazines (**229**) and their enantiomers (92EUP514267). Reduction of 6,8-diazabicyclo[3,2,1]oct-6-enes (**230**), prepared from **228** (R = Ph, R<sup>1</sup> = H) with alkyl or phenyl lithium in a mixture of acidified methanol and THF (pH = 3) with NaBH<sub>3</sub>CN under reflux gave 1-amino-1-substituted 4-phenylperhydropyrido[2,1-*c*][1,4]oxazines (**231**) (92EUP514267; 96

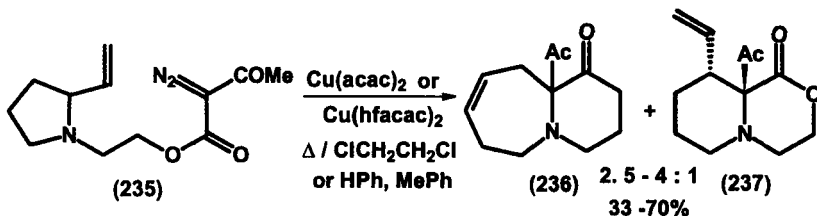


JOC6700). The 1-methyl derivative of **231** ( $R^1 = \text{Me}$ ) was accompanied by 10% of the C-1 epimer. Reduction of oxazolo[3,2-*a*]pyrimidine-5-carboxylates **232** with  $\text{Zn}(\text{BH}_4)_2$  gave an epimeric mixture of 4-phenylperhydropyrido[2,1-*c*][1,4]oxazin-1-one (**233**) (94JOC3769). When **232** reacted with  $\text{BF}_3$ -etherate at  $-10^\circ\text{C}$  in THF, then with Grignard reagents at  $-78^\circ\text{C}$ , epimeric mixtures of 4-phenyl-6-substituted perhydropyrido[2,1-*c*][1,4]oxazin-1-ones (**234**) were isolated after treatment with 2N HCl.

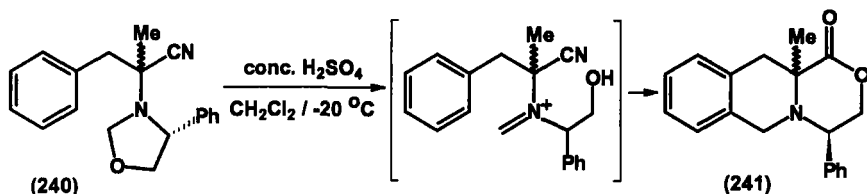
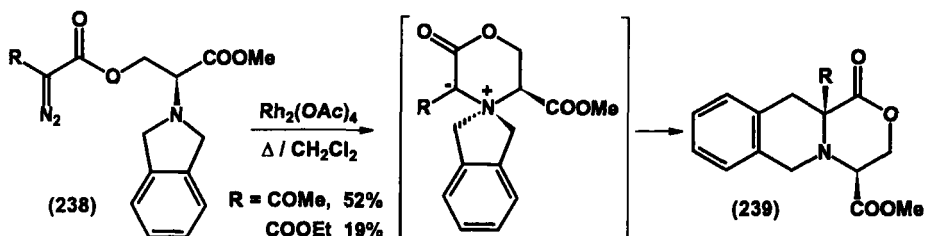


Diazodecomposition of  $\alpha$ -diazooester **235** with several copper carboxylate catalysts afforded azocyclooctene **236** along with perhydropyrido[2,1-*c*][1,4]oxazin-1-one **237** (96TL2165). Diazoesters **238** were subjected to the action of  $\text{Rh}_2(\text{OAc})_4$  to give optically active methyl (4*S*,11*aS*)-1-oxo-1,3,4,6,11,11*a*-hexahydro[1,4]oxazino-[4,3-*b*]isoquinoline-4-carboxylates (**239**) (95SL237). Treatment of a mixture of **240** with conc.  $\text{H}_2\text{SO}_4$  gave an epimeric mixture of 1,3,4,6,11,11*a*-hexahydro[1,4]oxazino[4,3-*b*]isoquinolin-1-ones (**241**) (87JHC1235).

From the reaction mixture of electrochemical oxidation of 2,3,4-trihydroxybenzophenone in MeOH containing tetraethylammonium perchlorate and an excess of tris(hydroxymethyl)aminomethane at a stationary



platinum electrode, 7-benzoyl-4,4-bis(hydroxymethyl)-3,4-dihydro-1*H*,6*H*-pyrido[2,1-*c*][1,4]oxazine-1,6-dione was isolated in 15% yield, as a result of an intramolecular rearrangement of a transient orthoquinone (95T4953).

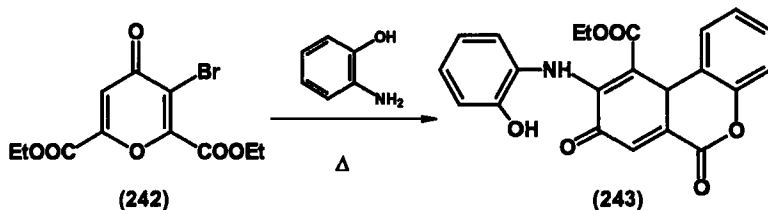


Reaction of 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine-4,5-dicarboxylic anhydride with diethyl malonate in the presence of 60% NaH in *N,N*-dimethylacetamide at 120°C afforded ethyl 7-hydroxy-9-nitro-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (93MIP4). 9-Chloro-2,3-dihydro-7-hydroxy-6-(*N,N*-disubstituted thiocarbamoyl)-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-5-ones were prepared from 7-chloro-3,4-dihydro-2*H*-1,4-benzoxazine-4,5-dicarboxylic anhydride with 3-(*N,N*-disubstituted amino)-3-thioxopropionates in the presence of 60% NaH in *N,N*-dimethylacetamide (95MIP5).

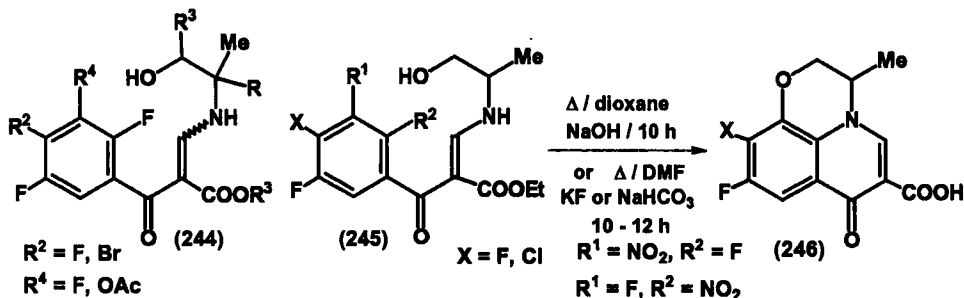
## 8. Miscellaneous

Pyrido[2,1-*c*][1,4]oxazine-1,4-dione derivatives were obtained in the base-catalyzed degradation of rapamycin and FD-506 (89TL671; 90

EUP364031; 93TL3699). Cyclocondensation of diethyl chelidonate and its 3-bromo derivative **242** with *o*-aminophenol afforded pyrido[2,1-*c*]-[1,4]benzoxazines **187** [85IJC(B)182] and **243** (89MI7), respectively.



Treatment of 2-aroil-3-aminoacrylates (**244**), or their *O*-(dimethyl-*tert*-butylsilyl) (88TL1931), and *O*-acetate derivatives (96USP5539110) with KF in DMF, with NaH, or with some other base, yielded 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates or 6-carboxylic acids (e.g., **194**, X = O, R<sup>1</sup> = H, R<sup>4</sup> = Me) [86CPB4098; 87GEP3522405, 87GEP3543513, 87JAP(K)87/215591; 88EUP271275, 88EUP287951, 88GEP3711193, 88JMC1694, 88USP4777253; 89EUP306860, 89GEP3913245, 89JAP(K)89/09992; 90JAP(K)90/264724, 90MIP2; 93BMC1711; 94CPB2063, 94CPB2569, 94CPB2629; 96GEP4428020; 97H(45)137]. Cyclization of 2-aroil-3-aminoacrylates (**245**) [91CCC1937; 97H(45)137] or their *O*-acetates (96USP5539110) led to pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids (**246**).

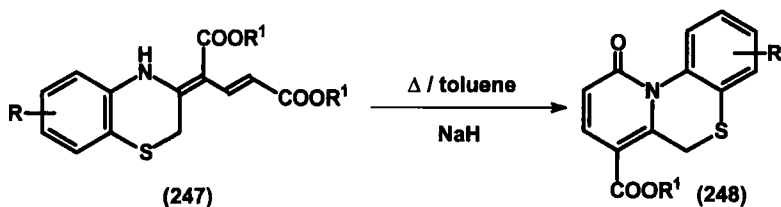


## B. PYRIDO[2,1-*c*][1,4]THIAZINES AND THEIR BENZO DERIVATIVES

### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6 + 0( $\alpha$ )]

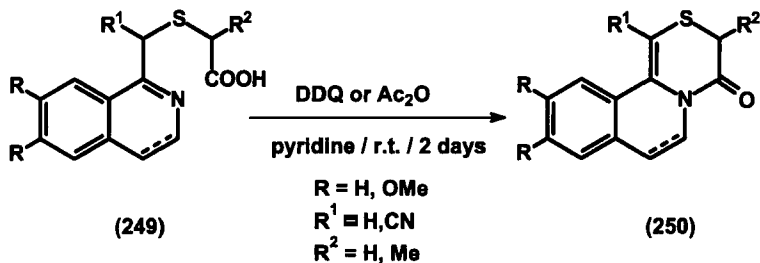
Perhydropyrido[2,1-*c*][1,4]thiazine was prepared when 2-[(2-hydroxyethylthio)methyl]piperidine was treated with HBr in AcOH, and the evaporated reaction mixture was treated with NaOEt in EtOH [57N559;

59AP(292)165]. Cyclization of ethyl 2-(2-piperidylmethylthio)acetate on the action of Na in boiling toluene afforded perhydropyrido[2,1-*c*][1,4]-thiazin-4-one [72OMR(4)283]. Ethyl 6-oxoperhydropyrido[2,1-*c*][1,4]thiazine-4-carboxylate was obtained by cyclization of methyl 4-(5-ethoxycarbonyl-1,4-thiazin-3-yl)butyrate in boiling toluene in the presence of (1*S*)-(+)-10-camphorsulfonic acid [96MIP8].



Heating [1,4]benzothiazines (247) in toluene in the presence of NaH afforded 10-oxopyrido[2,1-*c*][1,4]benzothiazine-7-carboxylates (248) (90-FES589). It was reported that methyl (*E,Z*)-4-(3,4-dihydro-2*H*-1,4-benzothiazin-3-ylidene)-3,4-dialkoxycarbonylbut-2-enoates gave 10-oxo-10*H*-pyrido[2,1-*c*][1,4]benzothiazine-7,8-dicarboxylates in boiling toluene in the presence of *p*-TSA [85H(23)1619], but the structure was later questioned [87JCS(P1)1027].

Cyclization of [(1-isoquinolinylmethyl)thio]acetic acids (249) on the action of DDQ or Ac<sub>2</sub>O afforded [1,4]thiazino[3,4-*a*]isoquinolin-4-ones **250** (81GEP3023717). 1,2-Dihydro[1,4]thiazino[4,3-*a*]quinolin-1-ones were obtained from (2-quinolyl)methylmercaptoacetic acids by treatment with Ac<sub>2</sub>O in pyridine (73IJC1051).

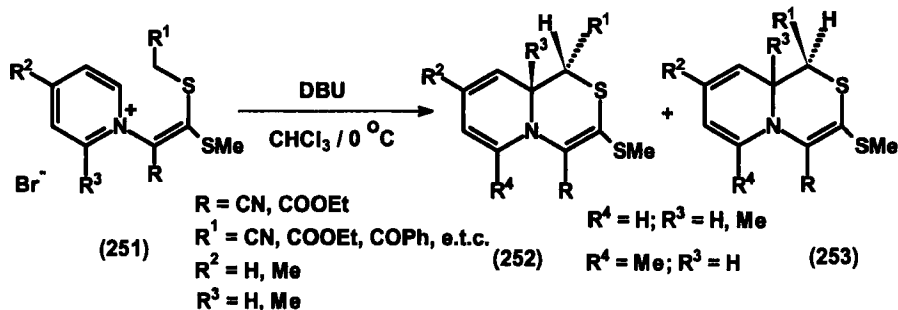


The 1,1-dioxide of 3-halomethyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium triiodide and bromide were prepared by cyclization of 8-allylsulfonylquinoline with I<sub>2</sub> in 2-PrOH, and with Br<sub>2</sub> in CHCl<sub>3</sub> (93MI9). When 8-[(1-chloro-2-mercapto-2-propyl)thio]quinoline HCl was left to stand in EtOH at 20°C 2-mercapto-2-methyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium chloride was obtained (94ZOR636). 8-[2-Chloro-1-(un)-substituted ethylthio]quinolines could easily cyclized to 2,3-dihydropyrido-

[1,2,3-*de*]-1,4-benzothiazinium chloride and its 3-methyl and phenyl derivatives [64JPR(25)279, 64MI2; 66JPR(32)235]. The unsubstituted derivative could not be prepared by the reaction of 8-mercaptoquinoline and 1,2-dibromoethane (60JA5013).

## 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6 + 0 ( $\beta$ )]

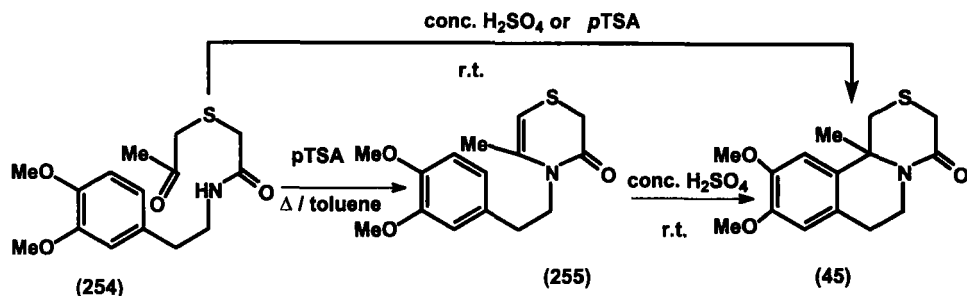
A 6-*endo*-trig mode of ring closure of 4-(3-butenyl)-3-hydroxythiomorpholin-5-one (**166**, R = H, X = S) in formic acid at room temperature led to the formation of perhydropyrido[2,1-*c*][1,4]thiazin-4-one (**167**, R = H, X = S) (81EUP34015; 83TL91). No 5-*exo*-trig ring closure was observed. Similarly, cyclization of 4-(3-methyl-3-butenyl)-3-hydroxy-5-oxotetrahydro-1,4-thiazine in formic acid afforded a 4 : 1 mixture of the C-8 epimers of 8-formyloxy-8-methylperhydropyrido[2,1-*c*][1,4]thiazin-4-one (85T2007).



The action of DBU on pyridinium bromides **251** (R<sup>3</sup> = H) instantly gave a *cis-trans* mixture of unstable 1,9*a*-dihydropyrido[2,1-*c*][1,4]thiazines (**252**, R<sup>3</sup> = R<sup>4</sup> = H) and (**253**, R<sup>3</sup> = R<sup>4</sup> = H) [85H(23)33; 87BCJ1867]. When DBU was replaced by K<sub>2</sub>CO<sub>3</sub> as a base, only intractable tarry materials were formed. The corresponding reactions of 2-methyl derivatives (**251**, R<sup>3</sup> = Me) led to more complex reaction mixtures, usually containing an isomeric mixture of (**252**, R<sup>3</sup> = H, R<sup>4</sup> = Me and R<sup>3</sup> = Me, R<sup>4</sup> = H) and (**253**, R<sup>3</sup> = H, R<sup>4</sup> = Me and R<sup>3</sup> = Me, R<sup>4</sup> = H) (87BCJ1867).

Ring closure of **176** (X = S, R = R<sup>1</sup> = H) in boiling DMSO yielded [1,4]thiazino[4,3-*a*]quinoline **107** (X = S, R = R<sup>1</sup> = H) (95TL5159). Heating 2-thioacetamide **254** in the presence of an acid yielded 1,2,4,6,7,11*b*-hexahydro[1,4]thiazino[3,4-*a*]isoquinolin-4-one **45** (80JHC449; 81CP1101857). When a shorter reaction period was applied, the intermediate **255** could be isolated, which was cyclized under similar reaction conditions (80JHC449; 81CP1101857; 92KGS994). 4-[2-(4-Methylphenyl)-

ethyl]-5-methyl-2,3-dihydro[1,4]thiazin-3-one could not be cyclized (80 JHC449).

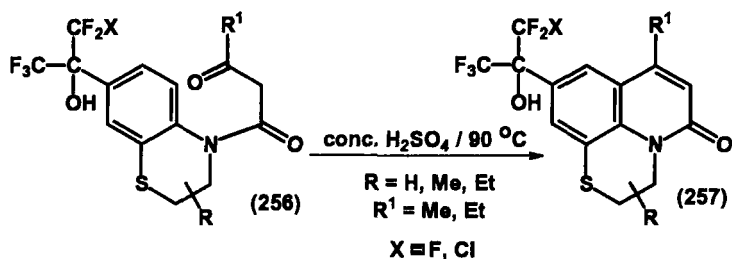


### 3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )]

Dieckmann cyclization of ethyl 4-[2-(ethoxycarbonyl)ethyl]-3-thiomorpholine-3-acetate and ethyl 4-(3-ethoxycarbonylpropyl)thiomorpholine-3-carboxylate on the action of *tert*-BuOK in Et<sub>2</sub>O, with subsequent acidic hydrolysis and decarboxylation, afforded octahydropyrido[2,1-*c*][1,4]-thiazin-8-one and -9-one, respectively (82EUP57536; 92BMC1293).

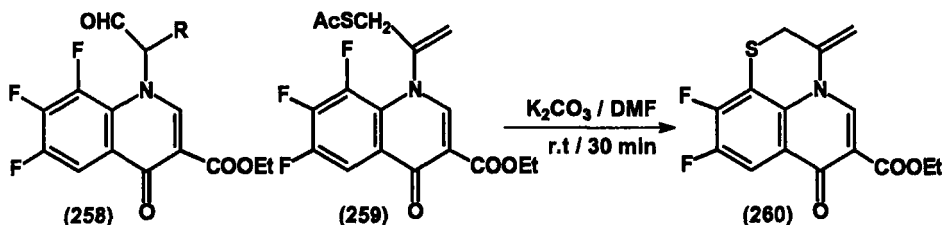
Cyclization of 2-(2-mercaptopropanoyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid by treatment with ethyl chloroformate in the presence of NEt<sub>3</sub> in CHCl<sub>3</sub> gave (3*S*,11*aR*)-*cis*-3,11*a*-H-3,11*a*-dimethyl-1,3,4,6,11,11*a*-hexahydro[1,4]thiazino[4,3-*b*]isoquinoline-1,4-dione (86-JMC784).

1,2,4,4*a*,5,6-Hexahydro[1,4]thiazino[4,3-*a*]quinoline-1,4-dione was prepared by cyclization of 1-(2-mercaptoacetyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid with diphenylphosphoryl azide in the presence of NEt(*i*-Pr)<sub>2</sub>Et in DMF at ambient temperature (81USP4273927).

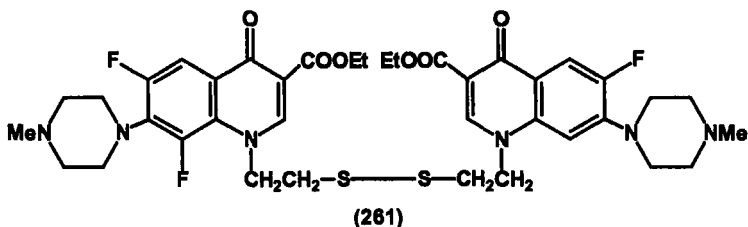


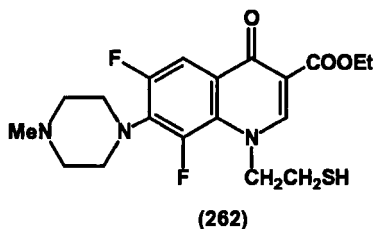
Heating 3-(3-oxo-3,4-dihydro-2*H*-[1,4]benzothiazin-4-yl)propionic acid in PPA at 120°C yielded 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzo-

thiazine-3,7-dione (72AJC1283). Cyclization of 4-(3-oxobutyryl)-3,4-dihydro-4*H*-[1,4]benzothiazin-5-ones in conc.  $\text{H}_2\text{SO}_4$  at room temperature afforded 7-methyl-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazin-5-ones (81JHC1273; 82JHC237). The 1,1-dioxides of the starting [1,4]benzothiazines could not be cyclized similarly (81JHC1273). 2,3-Dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazin-5-ones (**257**) were prepared by the cyclization of 3,4-dihydro-4-(1,3-dioxoalkyl)-2*H*-1,4-benzothiazines (**256**) in conc.  $\text{H}_2\text{SO}_4$  (79GEP2854725). 7-Oxopyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates (**112**) and (**260**) were obtained by the cyclization of quinoline-3-carboxylates **258** (91JHC1067) and **259** (91JHC1061) in the presence of NaSH and  $\text{K}_2\text{CO}_3$ , respectively. Cyclization of ethyl 1-[1-(1-chloromethyl)vinyl]-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate to **260** was unsuccessful with NaHS (91JHC1061).



Cyclization of (3,4-dihydro-2*H*-1,4-benzothiazin-4-yl)methylenemalonates (**193**, X = S) were carried out in PPA at 120–180°C [85 JAP(K)85/208987; 88EUP252352, 88EUP267432; 89EUP310969], on the action of PPE at 140–150°C (90EUP368410), in a mixture of  $\text{Ac}_2\text{O}$  and conc.  $\text{H}_2\text{SO}_4$  at 70–80°C (89EUP310969), and on the action of trimethylsilyl superpolyphosphate in boiling  $\text{CHCl}_3$  (90EUP376870). Rufloxacin ethyl ester was prepared by the reductive cyclization of bis(quinolinone) **261** on the action of NaH (60%) in DMF (95MIP1, 95MIP2), and on the action of  $\text{PPh}_3$  in the presence of a few drops of AcOH in  $\text{CH}_2\text{Cl}_2$ , followed by treatment with  $\text{K}_2\text{CO}_3$  in DMF (95MIP2), and by the cyclization of quinolone **262** with  $\text{K}_2\text{CO}_3$  in DMF (95MIP2).





#### 4. By Formation of Two Bonds from [5 + 1] Atom Fragments

Perhydropyrido[2,1-*c*][1,4]thiazine was prepared in the reaction of 1-(2-chloroethyl)-2-chloromethylpiperidine and  $\text{Na}_2\text{S}$  ( $\text{H}_2\text{O}$ )<sub>9</sub> in boiling aqueous EtOH (59CB1510). Cyclization of ethyl 7-substituted 6,8-difluoro-1-[1-bromo- and 1-(methylsulphonyloxy)-2-propyl]-1,4-dihydro-4-oxoquinoline-3-carboxylates with  $\text{EtOCS}_2\text{K}$  in DMF (94CPB2569), and in the presence of  $\text{H}_2\text{S}$  and  $\text{NaH}$  (89EUP306860), or by treatment with  $\text{MeCOSK}$  in DMF (93BMC1711) gave ethyl 10-substituted 9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyridol[1,2,3-*de*][1,4]benzothiazine-6-carboxylates.

#### 5. By Formation of Two Bonds from [4 + 2] Atom Fragments

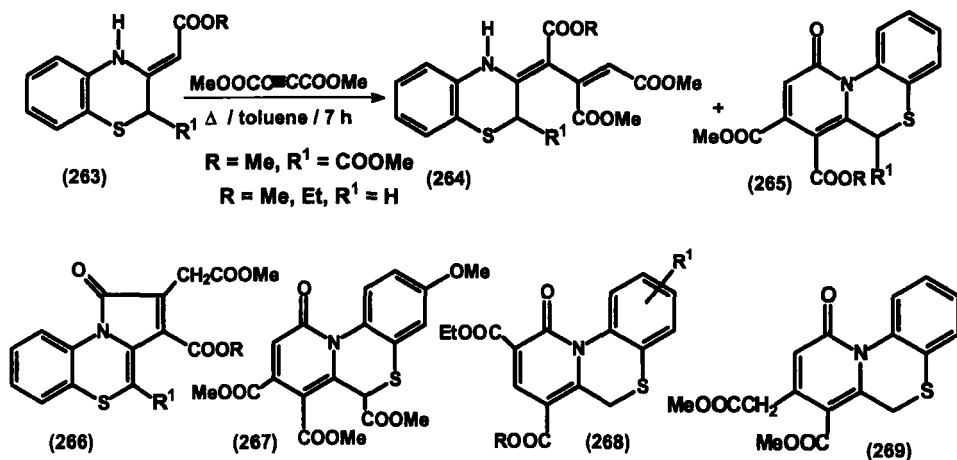
Reaction of 8-quinolinethiol with 1,2-dibromoethane (93MI7) and 2-bromoacetaldehyde or its diethyl acetal (93MI8) gave 2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium bromide and its 3-hydroxy derivative, respectively. 2-Mercapto-2-methyl-2,3-dihydropyrido[1,2,3-*de*]-1,4-benzothiazinium salt was prepared in the reaction of 8-quinolinethiol HCl with bromo- and chlorothioacetone in DMF or EtOH (94KGS570; 95SUL281). The reaction of 3-ethoxy-5,6-dihydro-2*H*-[1,4]thiazine and dimethyl acetylenedicarboxylate (DADC) in the presence of  $\text{NEt}_3$  at ambient temperature for 1 week furnished methyl 6-oxo-8-hydroxy-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]thiazine-9-carboxylate (72IJC323). 2-Ethoxycarbonyl-4,6-diphenylpyrylium tetrafluoroborate reacted with 2-mercaptoethylamine to give 6,8-diphenyl-1-oxo-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]thiazin-5-ium salt (84JHC1609). The cycloaddition of 3-[mercapto(methylthio)methylene]-1,2,3,4-tetrahydroisoquinoline-1,4-dione and DMAD in the presence of  $\text{K}_2\text{CO}_3$  yielded dimethyl 1-methylthio-6,11-oxo-3,4,6,11-tetrahydro[1,4]thiazino[4,3-*b*]isoquinoline-3,4-dicarboxylate (74YZ607).

#### 6. By Formation of Two Bonds from [3 + 3] Atom Fragments

Trapani *et al.* reported that the reactions of 3-alkoxycarbonylmethylene-3,4-dihydro[1,4]benzothiazines (263) with DMAD in boiling toluene gave



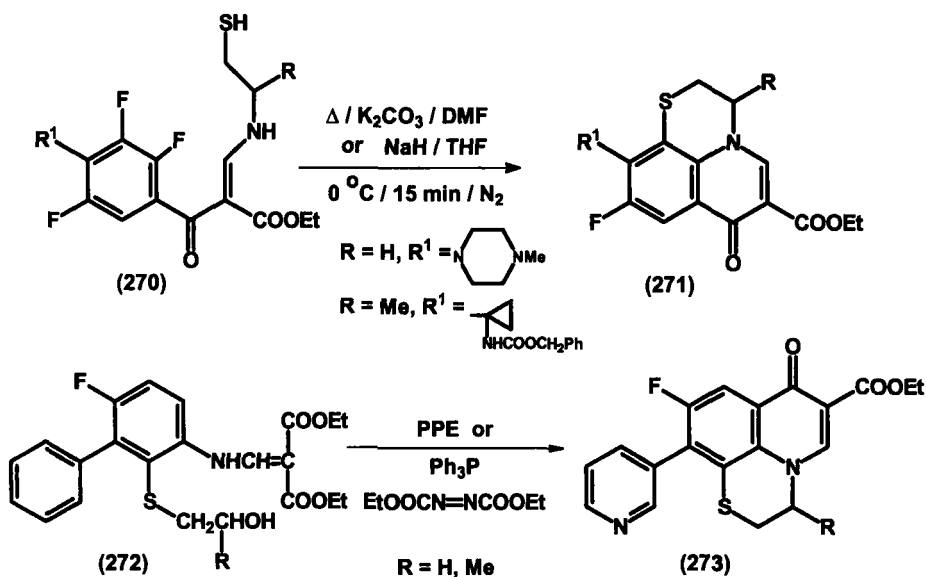
mixtures of addition (**264**) and ring-closed products [85H(23)1619]. The latter were described as pyrido[2,1-*c*][1,4]benzothiazin-10-ones (**265**), but the structure was later corrected on the basis of X-ray evidence to be pyrrolo[2,1-*c*][1,4]benzothiazin-1-ones (**266**) [87JCS(P1)1027]. Finally a pyrido[2,1-*c*][1,4]benzo-thiazin-10-one (**267**) was isolated in 10% yield from the reaction mixture of the 7-methoxy derivative of **263** ( $R = \text{Me}$ ,  $R^1 = \text{H}$ ) and DMAD (90FES577). It was claimed that only pyrido[2,1-*c*][1,4]benzothiazin-4-one (**265**,  $R = \text{Et}$ ,  $R^1 = \text{H}$ ) was formed in good yield when the ethyl ester (**263**,  $R = \text{Et}$ ,  $R^1 = \text{H}$ ) reacted with DMAD in MeOH containing AcOH under reflux for 2 h, and then at ambient temperature for 16 h (86USP4576942).



6-Oxo-3,4-dihydro-1*H*-pyrido[2,1-*c*][1,4]oxazine-9-carboxylate and 7,9-dicarboxylate were prepared from 3-(ethoxycarbonylmethylene)thiomorpholine with methyl propiolate and diethyl ethoxymethylenemalonate (EMME), respectively, at 190°C (90FES589). Pyrido[2,1-*c*][1,4]-benzothiazin-4-ones **248**, **268**, and **269** were prepared in the reactions of compounds **263** ( $R^1 = \text{H}$ ) and their benzo ring-substituted derivatives with methyl propiolate, EMME and 1,3-dimethoxycarbonyl-1,2-propanediene, respectively (90FES589). Reactions of 3,4-dihydro-4*H*-[1,4]benzothiazines with triethyl methanetricarboxylate at 150–200°C, and with EMME at 120–150°C for 2 h, and subsequent treatment of the reaction mixtures with PPA at 120°C for 1 h, afforded 7-hydroxy-5-oxo-2,3-dihydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates (93MIP4) and ethyl 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates (87JMC465; 93JMC3449), respectively. The reaction of 3-hydroxypyridine-2-thione and 1-bromo-3-chloropropane in boiling toluene gave 9-hydroxy-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium bromide [81JCR(M)2345, 81JCR(S)208].

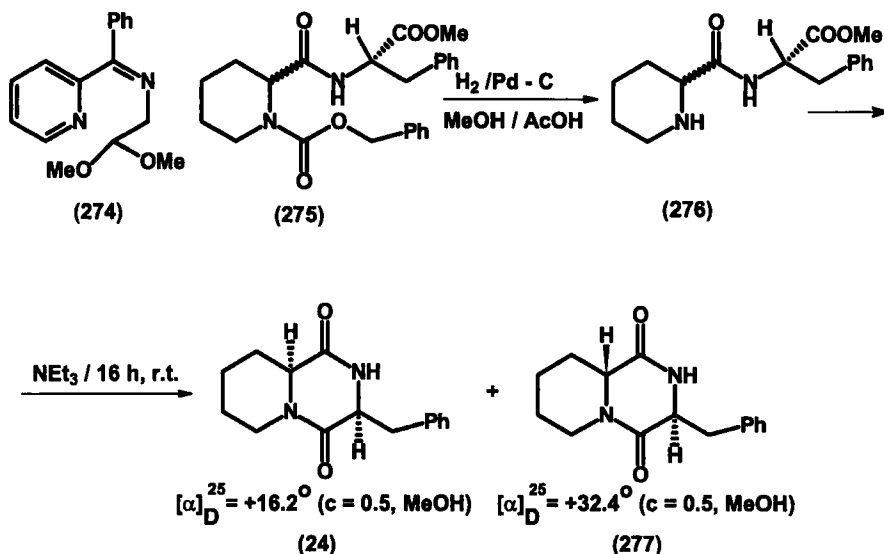
## 7. Miscellaneous

2,3-Dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates (**271**) were obtained by the cyclization of a mixture of the *E*- and *Z*-isomers of acrylates **270** on the action of NaH in THF at 0°C (89GEP3913245; 91SC2301; 93EUP522277). Cyclization of aryl aminomethylenemalonates **272** in PPE at 130–145°C and on the action of Ph<sub>3</sub>P and ethyl azodicarboxylate in THF at –20°C gave 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazoles **273** (87USP4636506).

C. PYRIDO[1,2-*a*]PYRAZINES AND THEIR BENZO DERIVATIVES1. By Formation of One Bond  $\alpha$  to the Bridgehead Nitrogen Atom [6 + 0( $\alpha$ )]

*a. From Pyridine Intermediates.* Treatment of 2-pyridyl anil **274** with 50% HBr in AcOH at –78°C gave 1-phenylpyrido[1,2-*a*]pyrazinium bromide [69JCS(C)2270]. Unsubstituted and 1-methyl derivatives could not be prepared by this route. The cyclization of *N*-(1-chloro-3-phenyl-2-propyl)-2-pyridinecarboxamide, prepared from (*S*)-phenylalanine, led to the verruculotoxin precursor 3-benzyl-1-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazinium chloride (76JA246). The 3-debenzyl derivative was prepared similarly [67NAT(L)(213)919] and also by heating *N*-(2-hydroxyethyl)picolinic acid amide in benzene in the presence of PBr<sub>3</sub> [67JCS(C)2391]. 3-Oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazinium chloride was obtained by the cyclization

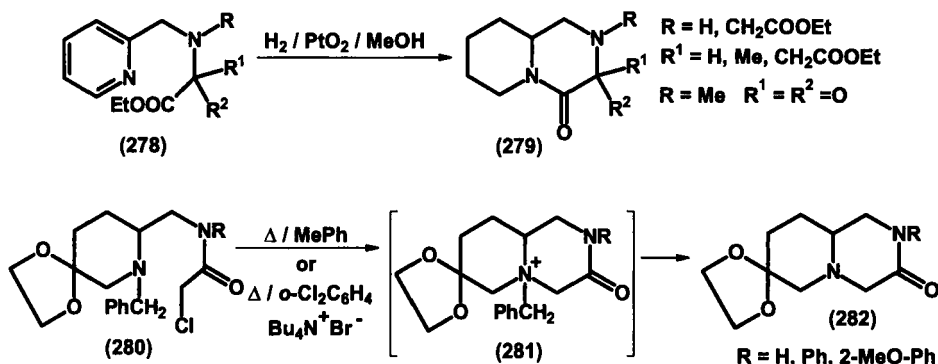
of 2-(chloroacetamidomethyl)pyridine in boiling EtOH (67YZ668). (+)- (4*R*,9*aS*)-4-Methyl-2-phenylperhydropyrido[1,2-*a*]pyrazine-3-one was obtained when 1-[(1*R*)-1-ethoxycarbonyl-ethyl]-(2*S*)-2-phenylaminomethyl-piperidine was treated with SiO<sub>2</sub>, or when the (2*R*)-epimer of the former compound was heated in boiling toluene with NaH (91TA231). The (–)-enantiomer of the bicycle was similarly prepared. Condensation of a racemic pipecolinic acid derivative with (*S*)-phenylalanine methyl ester (HCl) in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and NEt<sub>3</sub> afforded a mixture of diastereomeric dipeptides **275**, which was subjected to catalytic hydrogenolysis (88S963). After the hydrogenolysis, ring closure of **276** occurred by the action of NEt<sub>3</sub> to give a mixture of verruculotoxin (**24**) and its 8*a*-epimer **277**, which could be separated by column chromatography (88S963). Other pyrido[1,2-*a*]pyrazine-1,4-diones have also been similarly prepared (85BCJ497). Treatment of 1-*tert*-butoxycarbonyl-*N*-(alkoxycarbonylmethyl)pipecolinamides with CF<sub>3</sub>COOH, then heating the resultant oil in MeOH in the presence of NEt<sub>3</sub> gave racemic and optically active perhydropyrido[1,2-*a*]pyrazine-1,4-diones **48** (R = R' = H) (93 JMC2311; 94MIP2; 96MIP7).



Catalytic reduction of 2-aminomethylpyridine derivatives **278** over PtO<sub>2</sub> gave perhydropyrido[1,2-*a*]pyrazine-4-ones (**279**) [57N62; 59CB240; 65LA(685)181].

Perhydropyrido[1,2-*a*]pyrazine-3-ones (**282**) were formed when chloroacetyl derivatives **280** were heated in a high-boiling solvent in the presence

of  $\text{Bu}_4\text{N}^+\text{Br}^-$ , which may assist in the dequaternization of the intermediates **281** (91JOC5192).



1,2,3,4-Tetrahydropyrazino[1,2-*a*]quinolinium bromide was obtained from 2-[(2-bromo-1-oxoethyl)aminomethyl]quinoline by heating in acetone at  $100^\circ\text{C}$  in a sealed tube (63YZ679). The acid-catalyzed cyclizations of 2-[(2-hydroxyethyl)aminomethyl]-1,2,3,4-tetrahydroquinolines gave rise to 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines (47HCA920; 69GEP1901262, 69IJC833; 72JMC351; 74USP3829573). Treatment of 2-(*N*-*tert*-butoxycarbonyl-*N*-bromoacetylaminomethyl)-6-chloro-1,2,3,4-tetrahydroquinoline with  $\text{CF}_3\text{COOH}$  in  $\text{CH}_2\text{Cl}_2$  yielded 8-chloro-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolin-2-one (94MIP6; 96USP5576319).

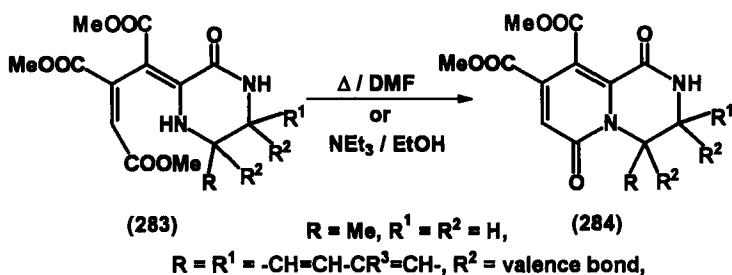
Cyclization of 1-[*N*-(2-haloacyl)-*N*-substituted aminomethyl]-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines in boiling EtOH, followed by catalytic hydrogenation over 10% Pd-C gave 9,10-dimethoxy-2-substituted 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-3-ones (71USP-3557120; 72USP3676444, 72USP3682926, 72USP3684813; 73USP3728352; 74USP3798223). 1,2,3,6,7,11*b*-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones were prepared by cyclization of *N*-(1,2,3,4-tetrahydroisoquinoline-1-methyl)glycines (75GEP2331713; 76GEP2441261, 76GEP2457971).

Cyclization of 8-[bis-(2-hydroxyethyl)amino]-6-methoxyquinoline with  $\text{POCl}_3$  afforded the 1-(2-chloroethyl)-9-hydroxy-1,2-dihydro-3*H*-pyrido[1,2,3-*de*]quinoxalinium salt (59JA3984). 2-Oxo-2,3-dihydro-1*H*-pyrido[1,2,3-*de*]quinoxalin-4-ium chlorides were formed when 8-(2-chloroacetamido)quinolines were heated to their melting points [68JHC371; 89JCS(P1)965]. 2-Methyl-3-ethoxycarbonyl- and 3-(*N*-phenylaminocarbonyl)-1*H*-pyrido[1,2,3-*de*]quinoxalinium chlorides were obtained from 8-[(2-(ethoxycarbonyl)- or *N*-phenylaminocarbonyl)-2-chloro-1-methylethenyl]-amino]quinoline in boiling toluene [76AP(309)966]. 8-(1-Ethoxycar-

bonylethyl)amino-6-methoxyquinoline underwent catalytic hydrogenation over Pd-C in AcOH to form 2-methyl-9-methoxy-3,5,6,7-tetrahydropyrido[1,2,3-*de*]quinoxalin-3-one [81IJC(B)331]. Heating 8-(chloroacetamido)-3-(dialkylamino)-1,2,3,4-tetrahydroquinolines, prepared from 8-amino-3-(dialkylamino)-1,2,3,4-tetrahydroquinolines with chloroacetic anhydride, in DMF at 150°C gave 6-(dialkylamino)-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxalin-2-ones (90MIP3). During the catalytical hydrogenation of ethyl 1-(2-azido-1-methylethyl)-7-(2,6-dimethyl-4-pyridinyl)-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate over Pd in DMF ethyl 9-fluoro-10-(2,6-dimethyl-4-pyridinyl)-3-methyl-7-oxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylate formed (93BMC 1711).

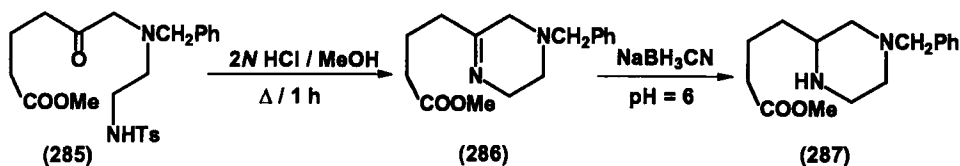
It was thought that acidic cyclization of 2-(1,2,3,4-tetrahydroxybutyl)quinoxaline yielded 8*H*-pyrido[1,2-*a*]quinoxalin-8-one, but later it was clarified that the product was 2-(2-pyrrolyl)quinazoline (61CH1191).

b. *From Pyrazine Intermediates.* The reaction products **283** of 1,2-diamines and *o*-phenylenediamines with DMAD underwent cyclization to pyrido[1,2-*a*]pyrazine-1,6-diones **284** ( $R = \text{Me}$ ,  $R^1 = \text{H}$ ) and pyrido[1,2-*a*]quinoxaline-6,10-diones **284** [ $R = R^1 = \text{CH}=\text{CHCR}^3=\text{CH}-$ ,  $R^2 = \text{valence bond}$ , and  $R = R^1 = (\text{CH}_2)_4$ ] under thermal and basic conditions [83H(20)1721; 87CPB457; 89JHC847]. Cyclization also occurred in low yields on photolysis.



2-Benzylperhydropyrido[1,2-*a*]pyrazin-6-one was prepared through the cyclization of **287**, obtained from **285** via **286** (93JOC690). From the reaction mixture of 2,3-di(2-tetrahydrofuryl)piperazine, treated with HBr gas in AcOH at 90–95°C, then with KOH, 1-(2-tetrahydrofuryl)-9-hydroxyperhydropyrido[1,2-*a*]pyrazine could be isolated (61BSF2135). Cyclization of 2-(1,2,3,4-tetrahydroxybutyl)quinoxalines in an acidic media gave 8*H*-pyrido[1,2-*a*]quinoxalin-8-ones together with a small amount of their 9-

hydroxy derivatives (35CB1716). The reductive cyclization of 4-(2-oxo-1,2-dihydro-3-quinoxaliny)butyric acid in 1N NaOH solution with NaBH<sub>4</sub> at room temperature furnished 5,6*a*,7,8,9,10-hexahydro-6*H*-pyrido[1,2-*a*]-quinoxaline-6,10-dione (65JA1990). Hydrogenation of ethyl 3-(2-oxo-1,2,3,4-tetrahydro-5-quinoxaliny)acrylate over Pd-C in the presence of *p*-TSA · H<sub>2</sub>O in a 1:1 mixture of MeOH and EtOH under 40 psi gave 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,5-dione (96JMC4654).

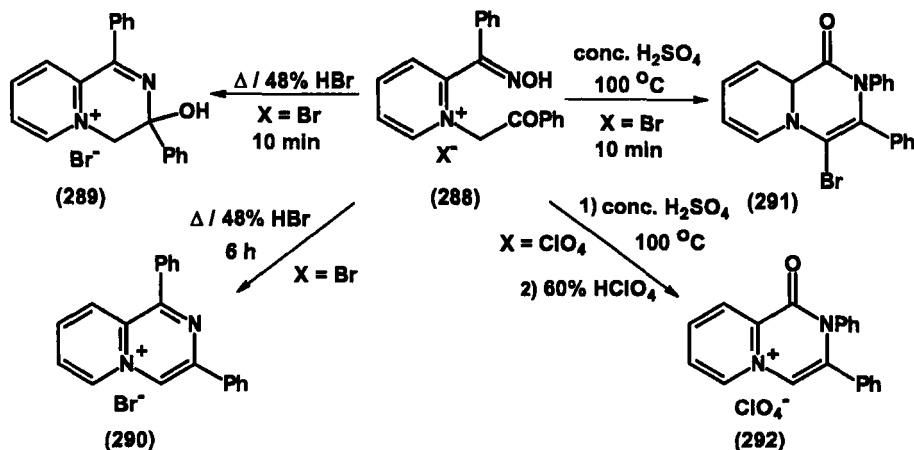


Heating dinitriles **176** ( $X = \text{NR}^2$ ) in boiling 1-butanol gave 2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines **107** ( $X = \text{O}$ ) (87S641).

### 3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )]

a. *From Pyridine Intermediates.* Treatment of 1-[2-(*N,N*-diethylamino)-ethyl]-2-hydroxymethyl-5-ethoxypyridin-4(1*H*)-one with  $\text{SOCl}_2$  gave 2,2-diethyl-7-ethoxy-8-oxo-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazinium chloride hydrochloride (60USP2965641). 1-(2-Methylaminoethyl)-5-benzyloxy-4-oxo-1,4-dihydropyridine-2-carboxylic acid was converted to 7-benzyloxy-2-methyl-2,3,4,8-tetrahydro-1*H*-pyrido[1,2-*a*]pyrazine-1,8-dione in response to heat (74JMC1). The *N*-isopropyl and *N*-acetyl derivatives underwent only decarboxylation instead of cyclization. Ring closure of 1-(2-oximinoethyl)-2-(1,3-dioxolan-2-yl)pyridinium halogenides in conc.  $\text{H}_2\text{SO}_4$  or in conc.  $\text{HCl}$  at  $100^\circ\text{C}$  gave pyrido[1,2-*a*]pyrazin-5-ium halogenide 2-oxides [66JOC941; 67JCS(C)2391]. Further pyrido[1,2-*a*]pyrazin-5-ium halogenide 2-oxides were prepared by cyclization of 1-phenacyl-2-oximinomethylpyridinium and 1-(2-oximinoethyl)-2-(oximinomethyl)pyridinium halogenides (66JOC941). Cyclization of 2-aminocarbonyl-1-(carboxymethyl)pyridinium betaine in boiling 48%  $\text{HBr}$  yielded 1,3-dioxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazinium bromide [67-JCS(C)2391].

Cyclization of 1-(2-phenyl-2-oxoethyl)-2-[phenyl(hydroxyimino)-methyl]pyridinium bromide (**288**) in boiling 48%  $\text{HBr}$  for 10 minutes gave 3-hydroxy-1,3-diphenyl-3,4-dihydropyrido[1,2-*a*]pyrazinium bromide (**289**) (Scheme 11). When the reaction period was 6 h, 1,3-diphenylpyrido-

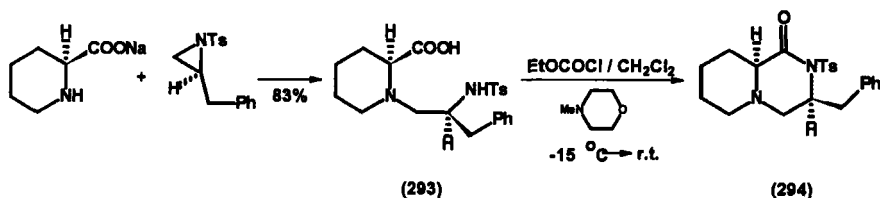


SCHEME 11

[1,2-*a*]pyrazinium bromide (**290**) was the product. Heating the starting bromide in conc.  $\text{H}_2\text{SO}_4$  at  $100^\circ\text{C}$  yielded 4-bromo-1-oxo-2,3-diphenyl-1,2-dihydropyrido[1,2-*a*]pyrazinium salt (**291**). When the perchlorate salt of the starting compound was treated with conc.  $\text{H}_2\text{SO}_4$  at  $100^\circ\text{C}$ , 1-oxo-2,3-diphenylpyrido[1,2-*a*]pyrazinium perchlorate (**292**) was obtained [71JCS(C)861]. Similarly, other 1,3- and 2,3-diaryl derivatives were prepared. 3-Aryl-2,6,7,8,9,9*a*-hexahydro-1*H*-pyrido[1,2-*a*]pyrazin-1-ones were obtained by cyclization of 1-(2-aryl-2-oxoethyl)pipecolic acid amides in boiling toluene in the presence of *p*-TSA (67NEP6613937).

Heating alkyl 6-substituted 1-[2-(*p*-nitrophenylcarbonylamino)ethyl]-pipecolates in boiling 6*N* HCl afforded 6-substituted perhydropyrido[1,2-*a*]pyrazin-1-ones (66JMC311, 68USP3388128).

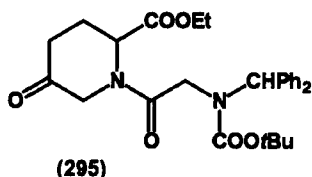
The reaction of *N*-[2-[*cis*-2,5-*H*- and *trans*-2,5-*H*-2,5-bis(methoxycarbonyl)-1-piperidyl]ethyl]phthalimides with  $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$  in MeOH afforded the respective methyl 1-oxoperhydropyrido[1,2-*a*]pyrazine-7-carboxylate (92MIP7, 92MIP8; 93MIP1, 93MIP7, =93MIP7; 95JHC857, 95TA321, 95USP545350). Similarly perhydropyrido[1,2-*a*]pyrazin-1-one was prepared from ethyl 1-(2-phthalimidoethyl)pipecolate in EtOH [91JAP(K)91/258720]. Hydrogenation of dimethyl *cis*-2,4-*H*-1-(cyanomethyl)piperidine-2,4-dicarboxylate (92MIP8) and a mixture of dimethyl *cis*- and *trans*-2,5-*H*-1-(cyanomethyl)piperidine-2,5-dicarboxylates (90MIP1; 92MIP1) over Raney Ni gave methyl *cis*-8,9*a*-*H*-1-oxoperhydropyrido[1,2-*a*]pyrazine-8-carboxylate and methyl *cis*-7,9*a*-*H*-1-oxoperhydropyrido[1,2-*a*]pyrazine-7-carboxylate, respectively. Methyl 1-oxo-2,6,7,8,9,9*a*-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-3-carboxylate was prepared from methyl 1-(2-methoxycarbonyl-2-nitrovinyl)pipecolate in a mixture of THF and *tert*-BuOH by reductive cyclization with a reagent, prepared from  $\text{HgCl}_2$  and  $\text{MgCl}_2$  in THF followed by  $\text{TiCl}_4$  (94T4887). Catalytic reduction of ethyl 1-cyanomethylpiperidine-2-carboxylate over Raney Ni in dioxane in the presence of  $\text{NEt}_3$  at 130 atm at  $130^\circ\text{C}$  led to perhydropyrido[1,2-*a*]pyrazin-1-one (67YZ668).



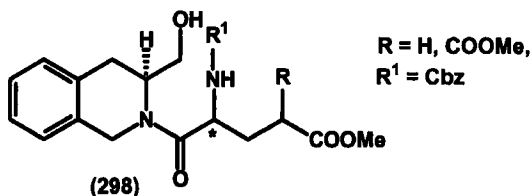
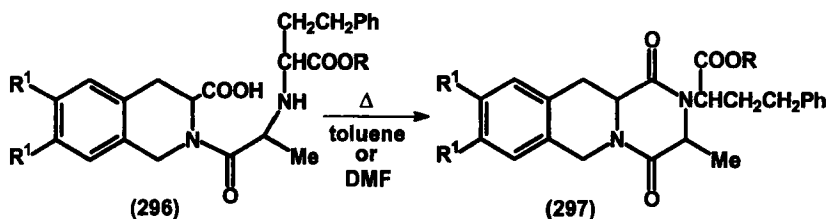
The *N*-tosyl derivative of verruculotoxin (**294**) was prepared by cyclization of the (*S*),(*S*)-enantiomer of amino acid **293** on the action of ethyl chloroformate in the presence of *N*-methylmorpholine (91TL1417). 2-*tert*-Butylperhydropyrido[1,2-*a*]pyrazin-3-one was prepared by reacting 2-(*N*-



*tert*-butylaminomethyl)piperidine with ethyl chloroacetate, followed by cyclization of the resultant 2-(1-piperidyl)acetate with Na in boiling toluene [72JCS(P2)1374].



Cyclodipeptides, bicyclic 2,5-dikeptopiperazines (such as **48**), containing pipecolic acid and other amino acids, were prepared by the cyclization of linear dipeptides [72CCC4060, 72TL1437; 73CCC1940; 91AX(B)92; 93AX(C)1113]. 7,8-Benzologues of **48** were similarly obtained starting from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) (92EUP517589; 96MIP6). Spontaneous formation of 3-[(4-hydroxyphenyl)methyl]-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione was observed in DMSO, MeOH, and acetone from peptides H-Tyr-Tic-NH<sub>2</sub>, H-Tyr-Tic-Phe-OH, and H-Tyr-Tic-Phe-Phe-NH<sub>2</sub> (93MI22; 95MI6), and its acid-catalyzed formation was studied under different conditions (95MI5). 1,4,7-Trioxo derivative **130** was obtained by treatment of **295** with HCl in AcOH, then heating in toluene (93BMC1233). Optically active 2-substituted 3-methyl-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones (**297**) were prepared from ACE inhibitor 2-substituted 1,2,3,4-isoquinoline-1-carboxylic acids and esters (**296**) (86JMC1953). This cyclization was later studied in more detail (87MI5; 88MI16; 89MI14; 90MI2, 90MI10; 92MI4, 92MI8).



Pyrazino[1,2-*b*]isoquinolin-5-ium 2-oxide perchlorate and its 3-methyl and 3-phenyl derivatives were obtained by cyclization of the appropriate 3-oximidomethyl-1-acylmethylisoquinolinium salt (or its oxime) through heating in an acidic medium (72JHC177). Swern oxidation of 2-acyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinolines (**298**) proceeded smoothly to yield a diastereomeric mixture of 1-hydroxy-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-4-ones **136** (87TL4065). Heating (3-carboxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetic acid in HCONH<sub>2</sub> at 120°C for 1 h, then at 160°C for 5 h yielded 1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,3-dione (88EUP296048). Treatment of 2-ethoxycarbonylmethyl-3-hydroxymethyl-6,7-dimethyl-4-phenyl-1,2-dihydroisoquinolin-1-one with MeSO<sub>2</sub>Cl in the presence of NEt<sub>3</sub>, then 2-methoxybenzylamine in THF at 130°C in a sealed tube afforded 2-(2-methoxybenzyl)-8,9-dimethyl-11-phenyl-1,2,3,4-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-3,6-dione (94EUP585913).

2-Benzoyl-1,2,3,6,7,11*b*-hexahydropyrazino[2,1-*a*]isoquinoline was obtained by cyclization of 1-benzamidomethyl-2-(2-chloroethyl)-1,2,3,4-tetrahydroisoquinoline (65BEP659249; 90URP1031169). Cyclization of 1-acylaminomethyl-2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinolines in the presence of a strong base gave 2-acyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones (75GEP2331713; 76GEP2441261; 77E1036, 77GEP1795728; 85MIP1; 91KGS1107). Cyclization of 1-benzamidomethyl-2-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline in HCl gave 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline-3-one (86MI3). 2-Benzoyl-3,3-dialkyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones were obtained by cyclization of 1-benzamidomethyl-2-(2-alkyl-2-bromopropionyl)-1,2,3,4-tetrahydroisoquinolines (91MI14). Heating 1-(*N*-substituted aminocarbonyl)-2-(2-haloacyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines in the presence of NaH in boiling toluene afforded 2-substituted 9,10-dimethoxy-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline-1,4-diones (71USP3557120; 72USP3676444, 72USP3682926, 72USP3684813; 73USP3728352; 74USP3798223).

Treatment of 1-chloroacetyl-2-(benzoylaminomethyl)-1,2,3,4-tetrahydroquinolines with 50% NaH in paraffin oil at 100°C for 3 days in a 4:1 mixture of dioxane and DMF yielded 2-benzoyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolin-4-ones (67SAP67/05764–67SAP67/05767). Acid-catalyzed cyclization of 1-(2-hydroxyethyl)-2-benzamidomethyl-1,2,3,4-tetrahydroquinoline gave 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (69IJC833). Treatment of 2-(*tert*-butoxycarbonylamino)methyl-1-(2-bromoacetyl)-7-trifluoromethyl-1,2,3,4-tetrahydroquinoline with CF<sub>3</sub>COOH, then with K<sub>2</sub>CO<sub>3</sub> in DMF yielded a 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (85JMC945). An epimeric mixture of perhydropy-

razino[1,2-*a*]quinolin-4-one was obtained from ethyl 1-(2-*p*-nitrobenzamidoethyl)-*cis*-decahydroquinoline-2-carboxylate on boiling in 6N HCl (64JOC326).

Cyclization of 1-(*o*-aminophenyl)-2-carboxy-4,6-diphenylpyridinium perchlorate in hot AcOH gave 8,10-diphenyl-6-oxo-5,6-dihydropyrido[1,2-*a*]quinoxalinium perchlorate (75KGS1578). The respective 5,6*a*,7,8,9,10-hexahydro-6*H*-pyrido[1,2-*a*]quinoxalin-6-one was prepared by hydrogen-transfer reductive cyclization of *N*-(*o*-nitrophenyl)piperidine-2-carboxylates or -2-carboxylic acid by heating in a mixture of cyclohexene over Pd-C and EtOH [82JHC1169; 83JHC1509; 88JCS(P1)1997]. Cyclizations were also carried out with Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> in aqueous solution at pH 9–10 [88JCS(P1)1997]. Reductive cyclization of 1-ethoxalyl-8-nitro-1,2,3,4-tetrahydroquinolines with 20% aqueous TiCl<sub>3</sub> solution in aqueous THF, acetone, or a mixture of AcOH and THF gave 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,3-diones (93MIP2; 94CP2121609, 94EUP627434, 94JMC3956; 95BMC1527, 95BMC1533). Cyclization of ethyl (*S*)-6,8-difluoro-7-(1-benzoyloxycarbonylamino-cyclopropyl)-1-[2-(*N*-methylamino)-1-methylethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate with K<sub>2</sub>CO<sub>3</sub> in DMF (89GEP3913245), or treatment of 6,8-difluoro-1-(2-bromo-1-methylethyl)-7-(1-benzoyloxycarbonylamino-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid with MeNH<sub>2</sub> in EtOH (94CPB2569) gave 10-(1-benzoyloxycarbonylamino-cyclopropyl)-7-oxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylate and acid, respectively.

b. *From Pyrazine Intermediates.* Dieckmann cyclization of (1,4-diacetyl-2-piperazinyl)acetonitrile in the presence of NaOEt afforded 2-acetyl-perhydropyrido[1,2-*a*]pyrazine-6,8-dione (64MI1). Reduction of 3-phenyl-4-(4-chlorophenacyl)-2-piperazinone with NaBH<sub>4</sub> in MeOH gave a mixture of 3-phenyl-4-[2-(4-chlorophenyl)-2-hydroxyethyl]-2-piperazinones, which were cyclized in conc. H<sub>2</sub>SO<sub>4</sub> at room temperature to give a 4.5 : 1 mixture of *trans*-7,11*b*-H- and *cis*-7,11*b*-H-7-(4-chlorophenyl)-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-1-ones [89H(29)359, 89JAP(K)89/31772]. When the starting 2-piperazinone was reduced with diborane and the reaction mixture was cyclized in conc. H<sub>2</sub>SO<sub>4</sub>, a 19 : 1 mixture of the preceding products was obtained [89H(29)359]. 2-Benzoyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones and their 7-oxo derivatives were prepared by cyclization of 1-benzoyl-4-(2-hydroxyethyl)-, and -4-(2-chloroethyl)-5-(4-methylphenyl)-3-oxopiperazines in HF, or in CS<sub>2</sub> in the presence of AlCl<sub>3</sub> (76GEP2441261, 76GEP2457971), respectively, and that of 1-benzoyl-4-(carboxymethyl)-, and -4-(chlorocarbonylmethyl)-5-aryl-3-oxopiperazine in HF, or in PhNO<sub>2</sub> in the presence of AlCl<sub>3</sub>, respectively (76GEP2441261). Cyclization of 3-aryl-4-(2-aryl-2-hydroxyethyl)piperazines in conc. H<sub>2</sub>SO<sub>4</sub> gave 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines (88USP4772705).

Heating 1-(3-bromopropyl)-1,2,3,4-tetrahydroquinoxaline hydrobromide or its 4-acetyl derivative in 8.8N HBr or in DMF afforded 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxalines (83KGS677, 83KGS682). Cyclization of dialkyl (1,2,3,4-tetrahydroquinoxalin-4-yl)methylenemalonates by PPA and PPE gave alkyl 7-oxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylates [80JAP(K)80/49379; 87USP4636506]. 1,2,3,5-Tetrahydropyrido[1,2,3-*de*]quinoxaline-2,5-dione was formed by cyclization and subsequent dearylation when 4-cinnamoyl-1,2,3,4-tetrahydroquinoxalin-2-one was treated with  $\text{AlCl}_3$  in 1,2-dichlorobenzene at 120°C (96JMC4654).

#### 4. By Formation of Two Bonds from [5 + 1] Atom Fragments

3-Substituted 2-oxo-1,2-dihydropyrido[1,2-*a*]pyrazinium salts were prepared from 1-(2-substituted 2-oxoethyl)-2-alkoxycarbonylpyridium salts by treatment with  $\text{AcONH}_4$  in boiling  $\text{AcOH}$  (90JHC1673). 2-Substituted perhydropyrido[1,2-*a*]pyrazines were prepared in the reactions of 2-chloromethyl-1-(2-chloroethyl)piperidine with primary amines (59CB1510; 66JMC311; 68USP3388128; 71GEP2029185, 71JPP71/34717; 72FRP 2092785, 72GEP2141464; 73CPB1248, 73JPP73/02559, 73JPP73/19597). 2-Ethyl-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-6-one was synthesized similarly from 2-(2-chloroethyl)-3-chloromethyl-1,2,3,4-tetrahydroisoquinolin-1-one [77IJC(B)70]. 2-Substituted 7-methoxy-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazin-8-ones were prepared from 1-(2-chloroethyl)-2-chloromethyl-5-methoxypyridin-4(1*H*)-one with primary amines (61USP2999860). When dialkylamine was used, 2,2-dialkyl quaternary salts were obtained.

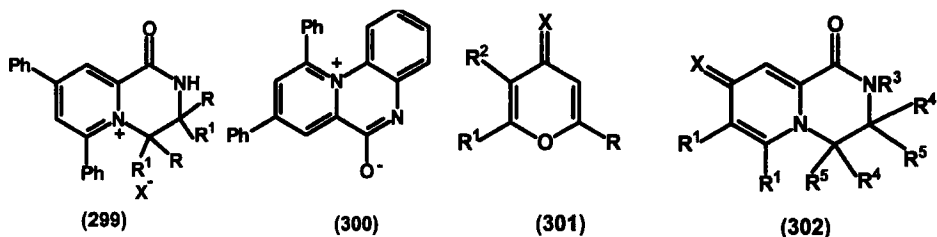
Reaction of 1-(ethoxycarbonylmethyl)-2-ethoxycarbonylpyridinium bromide with boiling aqueous  $\text{NH}_4\text{OH}$  gave 3,4-dihydro-1-hydroxy-3-oxo-pyrido[1,2-*a*]pyrazin-5-ium betaine [67JCS(C)2391]. Similar reaction of 1-(benzoylmethyl)-2-ethoxycarbonylpyridinium bromide and 1-(acylmethyl)-2-acylpyridinium salts with  $\text{AcONH}_4$  in boiling  $\text{AcOH}$  afforded 1-hydroxy-3-phenyl- and 1,3-disubstituted pyrido[1,2-*a*]pyrazinium salts, respectively (64CB3566). 2-[2-(3-Indolyl)ethyl]perhydropyrido[1,2-*a*]pyrazine-1,3-dione was obtained from methyl 1-(ethoxycarbonylmethyl)-pipercolate on heating with triptamine at 175°C (91T1065). The reaction of methyl 1-(chloroacetyl)piperidine-2-carboxylate and methanolic  $\text{MeNH}_2$  gave 2-methylperhydropyrido[1,2-*a*]pyrazine-1,4-dione [72JCS(P1) 2146]. 3-Benzyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline was prepared in the reaction of methyl 1-bromoacetyl-1,2,3,4-tetrahydroquinoline-2-carboxylate and  $\text{PhCH}_2\text{NH}_2$  (96MIP2). Reaction of ethyl 2-chloroacetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate with primary amines in boiling 2-ethoxyethanol gave 2-substituted 9,10-

dimethoxy-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline-1,4-diones (71USP3557120; 72USP3676444, 72USP3682926, 72USP3684813; 73USP3728352; 74USP3798223). 1-(Un)substituted 9-hydroxy-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrazin-8-ones and a 3-carboxylic acid derivative were prepared in the Pictet–Spengler cyclization of 1-(2-aminoethyl)- and 1-(2-amino-2-carboxyethyl)-3-hydroxy-1,4-dihydro-4-pyridone with aldehydes (78AJC187). The reaction of 1-acetyl-3-(2,5-dimethoxyphenylmethyl)-2,5-dioxopiperazine with MeCHO in a mixture of AcOH and CF<sub>3</sub>COOH under reflux furnished a mixture of *trans*-6,11*a*-H-2-acetyl-6-methyl-7,10-dimethoxy-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]-isoquinoline-1,4-dione and its 2-desacetyl derivative, both containing the 6-methyl group in the axial position (90AJC773).

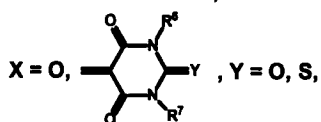
### 5. By Formation of Two Bonds from [4 + 2] Atom Fragments

a. *From Pyrones or Pyrylium Intermediates.* 2-Carboxy- [75KGS1578; 84KFZ(6)700; 87KFZ(3)292] and 2-ethoxycarbonyl-4,6-diphenylpyrylium salts (84JHC1609) reacted with ethylenediamine and *o*-phenylenediamine to yield 1-oxopyrido[1,2-*a*]pyrazinium (**299**, R = R<sup>1</sup> = H) and 6-oxopyrido[1,2-*a*]quinoxalinium salts [(**299**, R = double bond, and R<sup>1</sup> = —(CH = CH)<sub>2</sub>—)]. When the reaction was carried out in the presence of NEt<sub>3</sub> in the case of *o*-phenylenediamine, or when **299** [R = double bond, R<sup>1</sup> = —(CH = CH)<sub>2</sub>—] was treated with NEt<sub>3</sub>, the zwitterionic compound **300** could be prepared [84JHC1609, 84KFZ(6)700]. 6-Methyl-8,9-dimethoxy-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*b*]isoquinolinium perchlorate was prepared from 3-methoxycarbonyl-1-methyl-6,7-dimethoxybenzo[*c*]pyrylium perchlorate with ethylenediamine in boiling EtOH (74KGS342). Cyclocondensation of 3-formyl- and 3-carboxyl-1*H*-benzo[*c*]pyran-1-ones with ethylenediamine at ambient temperature, then in conc. HCl or an 1 : 1 mixture of conc. HCl and AcOH gave 11-phenyl-6-oxo-3,4-dihydro- and 11-phenyl-1,6-dioxo-1,2,3,4-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinolines, respectively (94EUP585913).

4*H*-Pyrone-2-carboxylic acids, their esters **301**, and **242** gave pyrido[1,2-*a*]pyrazine-1,8-diones **302** (R<sup>4</sup> = R<sup>5</sup> = H, X = O) and pyrido[1,2-*a*]quinoxaline-6,8-diones **302** [R<sup>4</sup> = valence bond, R<sup>5</sup> = —(CH = CH)<sub>2</sub>—, X = O] in the reactions with ethylenediamines and *o*-phenylenediamines, respectively [54JA1189; 56USP2740786; 65ZOR2222; 66AP(299)139; 74JMC1; 75AP(308)489; 85IJC(B)182; 89MI7; 90JHC1837]. 9-Hydroxy-5,6-dihydro-8*H*-pyrido[1,2-*a*]quinoxalin-8-one hydrochlorides were obtained in the reactions of kojic acid (**301**, R = CH<sub>2</sub>OH, R<sup>1</sup> = H, R<sup>2</sup> = OH, X = O) with *o*-phenylenediamines in conc. HCl at 95°C (75MI1; 86MI10).

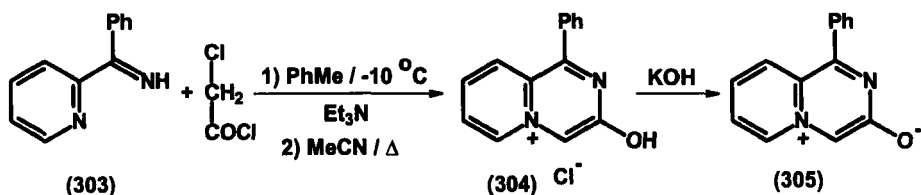


$R = \text{COOH, COOalkyl, } R^1 = \text{H, Ph, COOEt,}$   
 $R^2 = \text{H, OCH}_2\text{Ph, } R^3 = \text{H, Me, CH}_2\text{Ph, } R^4 = R^5 = \text{H,}$   
 or  $R^4 = \text{valence bond, } R^5 = -\text{CH}=\text{CR}_6-\text{CR}_6=\text{CH-},$

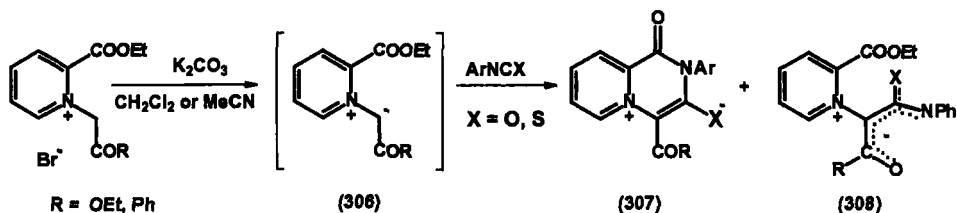


b. *From Pyridine Intermediates.* 1-Hydroxy-3-methyl-, 1-hydroxy-3-phenylpyrido[1,2-*a*]pyrazinium bromides and 1,3-dioxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazinium bromide were prepared in the reaction of 2-pyridinecarboxamide with 1-bromoacetone (90JHC1673),  $\omega$ -bromoacetophenone (64CB3566), and ethyl 2-bromoacetate [67JCS(C)2391], respectively. 1-Hydroxy-3-phenylpyrido[1,2-*a*]pyrazinium bromide was also obtained from 2-cyanopyridine with  $\omega$ -bromoacetophenone (64CB3566). Perhydropyridol[1,2-*a*]pyrazin-1-one was prepared in the reaction of methyl pipercolinate and ethyl imine in boiling EtOH (94MIP7, 94USP5354747; 95USP5461047). The reaction of phenyl (2-pyridyl) ketimine (**303**) with chloroacetyl chloride afforded 3-hydroxypyrido[1,2-*a*]pyrazinium chloride (**304**) (90JHC1673). Cyclocondensation of alkyl 2-pyridyl ketone oximes with bromoacetaldehyde in boiling MeCN gave 1-alkyl-3-hydroxy-3,4-dihydropyrido[1,2-*a*]pyrazinium bromide 2-oxides [71JCS(C)861]. 3-Methylpyridol[1,2-*a*]pyrazinium bromide 2-oxide, its 7,8- and 8,9-benzologues were obtained in the reaction of 2-pyridinealdoxime, its 4,5- and 3,4-benzologues with bromoacetone (66JOC941). The 1,3-dimethyl derivative was similarly prepared from 2-acetylpyridine oxime (66JOC941). 1,2-Dihydro-1-oxo-2,3-diphenylpyrido[1,2-*a*]pyrazinium salt was prepared in the reaction of 2-picolinanilide and phenacyl bromide in boiling MeCN [71JCS(C)861]. Pyrido[1,2-*a*]pyrazinium-1-olate **126** ( $R = \text{Me, Ph}$ ) and -3-olate **305** were obtained from 1-hydroxy-3-methylpyrido[1,2-*a*]pyrazinium bromide and **304** on the action of NaOH or KOH (64CB3566; 90JHC1673).

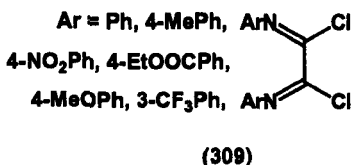
Cyclocondensation of ethyl 2-amino-2-(2-pyridyl)acetate and DMAD in boiling benzene afforded methyl 2-(1-ethoxycarbonyl-4-oxo-4*H*-pyrido-



[1,2-*a*]pyrazin-3-yl)acetate (93JHC1253). When the cyclocondensation was carried out in boiling MeOH and the reaction mixture was treated with NaOMe, the 1-methoxycarbonyl derivative was obtained (96JHC639). 1,4-Dipolar cycloaddition of *N*-ylides **306** with phenyl iso(thio)cyanates yielded 2-phenylpyrido[1,2-*a*]pyridinium-3-oxolates and -3-thiolates (**307**, Ar = Ph), together with small amounts of noncyclized products **308** (93T3185). Compounds **306** (R = OEt, X = O) and their 8,9-benzo derivatives were prepared from bis(ethoxycarbonylmethyl)pyridinium and isoquinolinium ylides by treatment with aryl isocyanates (71M1120).



Reactions of 2-aminomethylpyridine with bis(imidoylchlorides) **309** in THF in the presence of NEt<sub>3</sub> furnished 4*H*-pyrido[1,2-*a*]pyrazines **152** [96JPR(338)430]. 2-(*N*-Substituted aminomethyl)pyridines reacted with ethylene bromide in the presence of NEt<sub>3</sub> to produce 2-substituted 1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazinium bromides (68AF1431). Cyclocondensation of 2-pyridylmethylamine and oxalic acid bis(*p*-tolylimidoyl) chloride in THF in the presence of NEt<sub>3</sub> afforded 3-[(*p*-methylphenyl)amino]-4-[(*p*-methylphenyl)imino]-4*H*-pyrido[1,2-*a*]pyrazine [95JPR(337)38]. 1,2,3,6,7,11*b*-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines were prepared from 1-aminomethyl-1,2,3,4-tetrahydroisoquinolines on treatment with ethylene bromide (59YZ1003; 65BEP659249), or with ethylene glycol in the presence of Raney Ni at 200°C under 4 atm pressure of H<sub>2</sub> (65BEP659249).



Reactions of 3-substituted 2-(*N*-phenylaminomethyl)piperazines with a slight excess of ethyl 2-chloroacetate under reflux afforded mixtures of 9-substituted 2-phenylperhydropyrido[1,2-*a*]pyrazin-3- and -4-ones, which could be separated by column chromatography [72JCS(P2)1374]. When 2-[(3-trifluoromethylphenyl)aminomethyl]piperidine was heated with optically active ethyl 2-chloropropionate (87MIP1; 91TA231), or lactic acid ethyl ester methanesulphonate (91TA231), the product was a C-9a epimeric mixture of 2-(3-trifluoromethylphenyl)-4-methylperhydropyrido[1,2-*a*]pyrazin-3-ones. The reaction between *N*-methyl-2-piperidine-carboxamide and hydroxymaleic anhydride in pyridine resulted in 2,3-dimethyl-3-hydroxyperhydropyrido[1,2-*a*]pyrazine-1,4-dione (74CB2804).

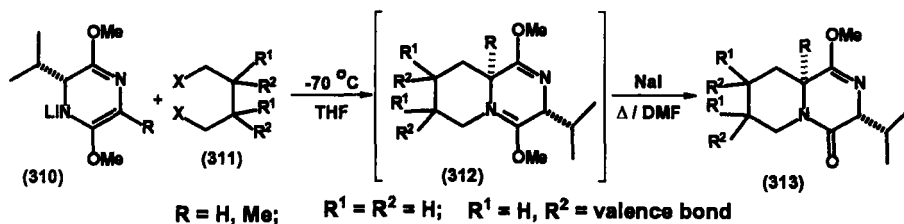
Reactions of bis(ethoxycarbonyl)methylpyridinium and isoquinolinium enol betaines with aryl isocyanates led to 2-aryl-4-ethoxycarbonyl-1-oxo-1,2-dihydropyrido[1,2-*a*]pyrazin-5-ium-3-olates and their 8,9-benzologues (71M1120). Perhydropyrido[1,2-*a*]pyrazine-3,4-dione was prepared in the reaction of 2-aminomethylpiperazine and diethyl oxalate in EtOH [65LA(685)181]. Reaction of 1-aminomethyl-1,2,3,4-tetrahydroisoquinolines with diethyl oxalate gave 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[1,2-*a*]isoquinoline-3,4-diones (65BEP659249; 84EUP107825, 84JMC995; 88USP4782058). Cyclocondensation of 1-(*N*-cyclohexylcarbonylamino-methyl)perhydroisoquinoline with chloroacetyl chloride afforded 2-cyclohexylcarbonylperhydropyrazino[2,1-*a*]isoquinolin-4-one (88KGS1115). Similarly, 2-acyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones were prepared from 2-acylamino-methyl-1,2,3,4-tetrahydroisoquinolines by treatment with chloroacetyl chloride (91KGS1107), and methyl chloroacetate (87MIP3). The 2-chloroacetyl derivative was obtained from 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline with 2 mol eq of chloroacetyl chloride (91KGS1107). Reactions of 2-aminomethyl-1,2,3,4-tetrahydroquinolines and 2-phenethylaminomethylperhydroquinoline with dialkyl oxalate gave 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline-1,2-dione s (47HCA920; 69GEP1901262, 69IJC833; 70JMC516; 71BRP1251821). Cyclocondensation of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline with diethyl fumarate in EtOH at room temperature gave rise to an isomeric mixture of 3-ethoxycarbonylmethyl-4-oxo- and 4-ethoxycarbonylmethyl-3-oxo-1,2,3,5,6,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolines (85KGS798).

Various 3,5,6,7-tetrahydropyrido[1,2,3-*de*]quinoxalines were obtained when 8-amino-1,2,3,4-tetrahydroquinoline was subjected to cyclocondensation with oxalyl chloride (60JOC1138; 65JOC2589), ethyl oxalyl chloride (65JOC2589; 90MIP3; 92JMC1076), benzil (38MI1), benzoin and its derivatives (60JOC1138; 65JOC2589), pyruvic acid (38MI1; 68JHC371), butyl glyoxylate (90MIP3; 92JMC1076), or 4-phenyl-2,4-dioxobutyric acid [78KFZ(7)89]. 6-(Dipropylamino)-1,2,3,5,6,7-hexahydropyrido[1,2-*a*]quinox-



alin-3-ones, accompanied by a small amount of 2-oxo isomers, were obtained from 3-(dialkylamino)-8-amino-1,2,3,4-tetrahydroquinolines with ethyl bromoacetate (90MIP3; 92JMC1076). Reactions of 8-aminoquinolines with  $\alpha$ -bromoketones and -acetaldehyde [68JHC371; 80CL951, 80H(14)1107; 89JCS(P1)945], and with  $\alpha$ -haloacid halides [89JCS(P1)965] afforded 2-(un)substituted 3*H*-pyrido[1,2,3-*de*]quinoxalinium bromides and 3-substituted 1,2-dihydro-3*H*-pyrido[1,2,3-*de*]quinoxalinium halides, respectively. 3,5,6,7-Tetrahydropyrido[1,2,3-*de*]quinoxalin-3-one-1-oxide was formed when 8-nitro-1,2,3,4-tetrahydroquinoline was treated with diketene in toluene in the presence of a catalytic amount of pyridine [85H(23)1729, 85JAP(K)85/84287].

c. *From Pyrazine Intermediates.* Reactions of 2-phenyl-5(4*H*)-oxazolon and 2-[(*E*)-2-dimethylaminoethenyl]pyrazine in boiling AcOH afforded 7-benzamido-6*H*-pyrido[1,2-*a*]pyridazin-6-one (91BSB533). The base-catalyzed reaction of  $\alpha$ -cyano-*o*-tolunitrile and 2-chloro-3-methylpyrazine in dry glyme gave 11-cyano-6-imino-1-methyl-6*H*-pyrazino[1,2-*b*]isoquinoline and its 6-oxo derivative in 2.8% and 4.35% yields, respectively (78JOC3536). Diastereoselective alkylation of optically active lithiated bis-lactim ethers **310** with 1,4-dihaloalkanes **311** resulted in their cyclization to intermediates **312**, which gave optically active pyrido[1,2-*a*]pyrazines **313** on treatment with 1 mol eq NaI [87AG(E)143; 88LA1025]. The dianion obtained from 2,3,5,6-tetraphenylpyrazine with Na in THF was reacted with 1,4-dichlorobutane at  $-78^\circ\text{C}$  to give 1,3,8,9-tetraphenyl-6,7,8,9-tetrahydro-9*aH*-pyrido[1,2-*a*]pyrazine (96RTC377). 8-Phenyl-10*H*-pyrido[1,2-*a*]quinoxalines and their 9-cyano and 9-ethoxycarbonyl derivatives were obtained in the reactions of 2-phenethynylquinoxaline with ethyl acetoacetate, ethyl cyanoacetate, and diethyl malonate, respectively in the presence of NaOEt [80JCS(P1)1384].

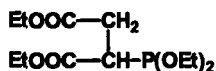


## 6. By Formation of Two Bonds from [3 + 3] Atom Fragments

Cyclocondensation of bromoacetaldehyde oxime with 2-benzoylpyridine and 2-cyanopyridine gave 1-phenylpyrido[1,2-*a*]pyrazin-5-ium bromide 2-

oxide and 1-imino-1,4-dihydropyrido[1,2-*a*]pyrazin-5-ium bromide 2-oxide, respectively [67JCS(C)2391]. Racemic and optically active perhydropyrido[1,2-*a*]pyrazin-1-ones [60JOC2108; 69JHC181; 73CPB1248; 83IJC(B)664] and their 7,8-benzologues [64JOC326; 73CPB2039; 75IJC230; 77IJC(B)70] were prepared from the respective alkyl 2-piperidinecarboxylate and its 4,5-benzologue with ethyleneimine. Reaction of methyl all-*cis*-perhydroisoquinoline-3-carboxylate with 2-bromoacetamide in DMF in the presence of  $K_2CO_3$ , then treatment of the reaction mixture with NaOMe in MeOH afforded perhydropyrazino[1,2-*b*]isoquinoline-1,3-dione (83USP4381302). 1,3,4,6,11,11*a*-Hexahydropyrazino[1,2-*b*]isoquinoline-1,4-diones were obtained in the reaction of ethyl 1,2,3,4-tetrahydroisoquinolines and  $N_3CH_2COCl$  in pyridine, then treatment with Zn-AcOH in a 9:1 mixture of  $CH_2Cl_2$  and MeOH (85TL2955).

Cyclocondensation of pipercolinic acid and malic acid anhydride in pyridine afforded 3-hydroxy-2,3-dimethylperhydropyrido[1,2-*a*]pyrazine-1,4-dione (74CB2804). Cyclocondensation of bis(2,4,6-trichlorophenyl) malonates with 2-methyl-, 2-benzyl- and 2-ethoxycarbonylmethylquinoxalines and -3-ones at 250°C afforded 8-hydroxy-10*H*-pyrido[1,2-*a*]quinoxalin-10-ones and their 5,6-dihydro-6,10-dione derivatives (77M103). Under Horner-Wittig reaction conditions, the reactions of 2-formylquinoxaline and dialkyl phosphonosuccinates (**314**) also involved cyclization to give alkyl 10-oxo-10*H*-pyrido[1,2-*a*]quinoxaline-8-carboxylate (80LA542).



(314)

Reaction of a 1 : 3 : 1 mixture of 3-methyl-2-quinoxalylmethyl carbanion (generated from 2-trimethylsilylmethyl-3-methylquinoxaline), perfluoro-2-methyl-2-pentene, and KF at  $-5^\circ\text{C}$  in THF, followed by refluxing for 6 h in xylene and then quenching with  $H_2O$ , gave 6-methyl-8-pentafluoroethyl-9-trifluoromethyl-10*H*-pyrido[1,2-*a*]quinoxalin-10-one (92NKK1455). Similarly, 7-trifluoromethyl-8-pentafluoroethyl-6*H*-pyrido[1,2-*a*]pyrazin-1-one was prepared from 2-(trimethylsilylmethyl)pyrazine [92MI10; 96JCR(M) 844, 96JCR(S)136]. 3-Ethoxycarbonylmethylene-1,2,3,4-tetrahydroquinoxalin-2-one and EMME underwent cyclocondensation at 190°C to afford diethyl 6,10-dioxo-5,6-dihydro-10*H*-pyrido[1,2-*a*]quinoxaline-7,9-dicarboxylate (90FES589). Cyclocondensation of 1,2,3,4-tetrahydroquinoxalines and their 3-oxo derivatives with EMME at 100–130°C in the presence of PPA afforded 7-oxo- and 2,7-dioxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxylic acids or their ethyl ester [80JAP(K)80/49379; 82USP

4348521]. 1-Acetyl-1,2,3,4-tetrahydroquinoxaline and 1,3-dibromopropane reacted at 130–140°C in the presence of CaO to give 1-acetyl-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline (83KGS677).

### 7. By Formation of Three Bonds from [2 + 2 + 2] Atom Fragments

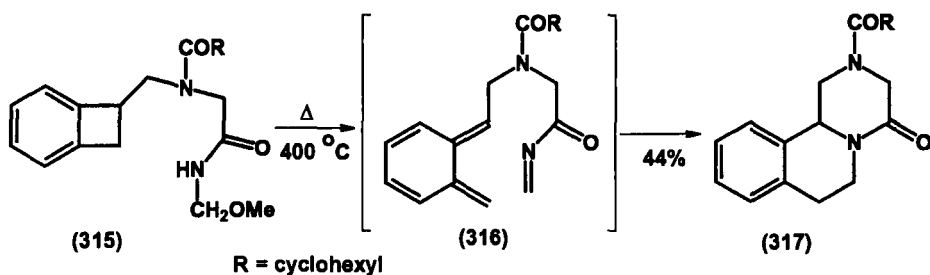
Reaction of quinoxaline with DMAD furnished tetramethyl -6*a*H-pyrido-[1,2-*a*]quinoxaline-7,8,9,10-tetracarboxylate (72MI1).

### 8. Ring Transformations

Schmidt reaction of pyrrolo[1,2-*a*]pyridin-2-one with hydrazoic acid in CHCl<sub>3</sub> at 0°C afforded perhydropyrido[1,2-*a*]pyrazin-3-one (68JOC2379). Treatment of tetraethyl 1-methyl-5-methylthio-1,2,3,5-tetrahydroimidazo-[1,2-*a*]pyridine-5,6,7,8-tetracarboxylate with EtNH<sub>2</sub> in an autoclave at 50°C gave rise to triethyl 2-methyl-6-ethylimino-1-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrazine-7,8,9-tricarboxylate (74HCA750). Tetraethyl 9*a*-ethyl-1-methyl-1,9*a*-dihydroimidazo[1,2-*a*]pyridine-5,6,7,8-tetracarboxylate on heating in AcOH gave 1,2-dimethyl-1,9*a*-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-6,7,8,9-tetracarboxylate and 6-ethylidene-2-methyl-1,6-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-7,8,9-tricarboxylate (62JCS1510). From the mixtures obtained on the reactions of immunomodulators, rapamycin, FK-506, PhCH<sub>2</sub>NH<sub>2</sub>, and NaBH<sub>3</sub>CN, 2-benzylperhydropyrido[1,2-*a*]pyrazine-1,4-dione was isolated in moderate yields (91JOC2900; 92TL7469). 1-(2-Tetrahydrofuryl)-9-hydroxyperhydropyrido[1,2-*a*]pyrazine was isolated from the reaction mixture of 2,3-bis(2-tetrahydrofuryl)piperazine in AcOH containing HBr (56BRP763990; 58FRP1167644). Hydrogenation of tetracyclic pyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[2,1-*c*]pyrazi-5,8-diinium salts over Adams catalyst at 3 atm gave a mixture of 2-(2-piperidylmethyl)perhydropyrido[1,2-*a*]pyrazine and its 1-oxo derivative [69JCS(C)-1987]. Ring transformation of spiro[2-oxo-1,2,3,4-tetrahydroquinoxaline-3,4'-1'-cyano-3'-ethoxycarbonyl-2'-hydroxy-2'-cyclobutene] in boiling DMF and treatment of the reaction mixture with AcOH, or by treatment guanidine hydrochloride in boiling AcOH, afforded 7-cyano-8-hydroxy-5,6-dihydro-10*H*-pyrido[1,2-*a*]quinoxaline-6,10-dione (83S1029; 84CPB3366).

Isomerization of benzo[*f*]-1,5-diazabicyclo[3,2,2]nonene in 8.8 N HBr at 140°C yielded 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline (83KGS677). Photolysis of dimethyl 1-(quinolin-8-yl)-1,2,3-triazole-4,5-dicarboxylates in MeCN resulted in stable *anhydro*-2,3-dimethoxycarbonyl-3*H*-pyrido[1,2,3-*de*]quinoxalin-4-ium hydroxides [87JCS(P1)403]. 6-Hydroxymethyl-2-methyl-7-methoxy-1,2,3,4-tetrahydro-6*H*-pyrazino-[1,2-*b*]isoquinolin-4-one (**138**) was prepared from 5-[[*N*-methyl-*N*-(ethoxy-

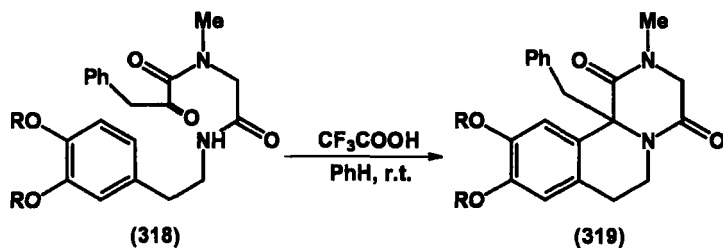
carbonylmethyl)amino]methyl]-10-methoxy-1,10*b*-dihydro-5*H*-oxazolo[2,3-*a*]-isoquinolin-3-one by treatment with 2*M* LiOH in EtOH, then with DCC in the presence of *N*-hydroxybenzotriazole in DMF (95JOC6791). Treatment of 2-(2-fluorophenyl)-2-trimethylsilyloxy-5-benzylperhydroisoxazolo[2,3-*a*]pyrazin-4-one with Mo(CO)<sub>6</sub> in boiling wet MeCN afforded 3-benzyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline-4,6-dione (96TL7343). The pyrolysis of benzocyclobutene derivative **315** led to the formation of 2-cyclohexylcarbonyl-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (**317**) via the internal Diels–Alder reaction of quinodimethane (**316**) (84JOC5269).



## 9. Miscellaneous

Perhydropyrido[1,2-*a*]pyrazin-1-one was prepared when ethyl 2,6-dibromocaproate and ethylenediamine were heated in EtOH in the presence of KI (68FRP1510781; 69BRP1144749, 69URP245789; 70ZOR1729). Reaction of diethyl acetonedioxalate and ethylenediamine gave 1,8-dioxo-2,3,4,8-tetrahydro-1*H*-pyrido[1,2-*a*]pyrazine-6-carboxylic acid (65ZOR2222). *trans*-6,9*a*-H-6-Cyanoperhydropyrido[1,2-*a*]pyrazin-1-one was isolated in 11% yield in the Strecker reaction of glutaraldehyde with ethylenediamine in the presence of NaHSO<sub>4</sub> and KCN [86H(24)2835]. 8-Hydroxy-3,4-dihydro-9*aH*-pyrido[1,2-*a*]pyrazine was isolated from the reaction mixture of sucrose and ethylenediamine in low yield (64MI1). The formation of 2,5-diketopiperazines (e.g., **48**) was observed during the thermal degradation of actinomycin D [71JCS(CC)39]. Cyclization of ethyl 3-[2-[(2-hydroxyethyl)amino]ethylamino]-2-(2,3,4,5-tetrafluorobenzoyl)acrylate in the presence of K<sub>2</sub>CO<sub>3</sub> in DMF at  $140^\circ\text{C}$  gave 1-(2-hydroxyethyl)-9,10-difluoro-7-oxo-1,2,3,7-pyrido[1,2,3-*de*]quinoxaline-6-carboxylate (87GEP3522406).

Treatment of phenylpyruvoyl derivatives **318** with CF<sub>3</sub>COOH gave hexahydropyrazino[2,1-*a*]isoquinoline-1,4-diones (**319**) [68JCS(CC)1450]. Ozonolysis of *N*-(3,4-dimethoxyphenethyl)-2-(*N*-ethoxycarbonyl-*N*-allyl-



amino)acetamide and work-up with  $\text{Me}_2\text{S}$ , followed by cyclization with formic acid, gave 2-ethoxycarbonyl-9,10-dimethoxy-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (85SC883). 1,2,3,6,7,11*b*-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones and their 2-acyl derivatives were obtained by cyclization of *N*-(2-arylethyl)-2-[(2,2-dimethoxyethylamino)]acetamides, their *N*-acyl derivatives, and *N*-phenethyl-*N*-(2,2-dimethoxyethyl)-2-(acetamino)acetamide in a strongly acidic medium (82GEP3324532; 85USP4497952). 9-Hydroxy-5,6-dihydro-8*H*-pyrido[1,2-*a*]quinoxalin-8-one hydrochloride was prepared from *o*-phenylenediamine dihydrochloride by reaction with *D*-*threo*-2,5-hexodiulose, and 5-oxofructose in  $\text{H}_2\text{O}$  [75MI1, 75JAP(K)75/04100].

## V. Applications and Important Compounds

### A. PYRIDO[2,1-*c*][1,4]OXAZINES AND THEIR BENZO DERIVATIVES

10-(Substituted amino)-9-fluoro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids are intensively investigated as antibacterial agents (84CPB4907; 87CPB1896; 88JMC1694, 88JMC2004, 88MI12; 90JHC1509, 90JMC2270; 91AAC442, 91CCC1937, 91CCC2406, 91JHC1061, 91JHC1067, 91JMC1142, 91MI1; 92AF70, 92CCC216; 93AAC2112, 93JMC801, 93JMC1356). Of these derivatives ofloxacin (**19**) (86CPB4098, 86MI8, 86MI9; 87MI4; 89MI13; 91MI7; 92MI22; 95MI7) and its optically active (*S*)-form, levofloxacin (**20**) (86AAC163; 87JMC2283; 89AAC1105; 94MI11, 94MI22) were introduced into human therapy, as highly active antibacterial agents against Gram-positive and Gram-negative pathogens, respectively. These types of compounds were also claimed to treat mycoplasma pneumonia in pigs (86MIP1). Pazufloxacin (**22**) is under development as an antibacterial agent (92AAC2293). 10-Aryl-9-fluoro-2-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acids exhibited activity against DNA topoisomerase II (93AAC646, 93BMC1711).

Immunosuppressive macrolides contain a pyrido[2,1-*c*][1,4]oxazine moiety (93USP5189042). 7*t*,8*c*,9*t*,9*ac*-H-7,8,9-Trihydroxyperhydropyrido[2,1-*c*]-[1,4]-oxazin-3-one was patented as an antiviral agent against retroviruses (89EUP315017). 8-Bromo- and 8-chloro-2,5,6,7-tetrahydro-3*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-3-ones were used in a synergistic fungicide composition (85GEP3333411, 85GEP3333412, 85GEP3333449).

Optically active pipecolic acid (94JOC3769) and its derivatives (90SL731; 92T431; 94JOC3769; 95TL1657; 96JOC5736, 96TL4001) were prepared via 4-phenylpyrido[2,1-*c*][1,4]oxazin-1-one derivatives.

### B. PYRIDO[2,1-*c*][1,4]THIAZINES AND THEIR BENZO DERIVATIVES

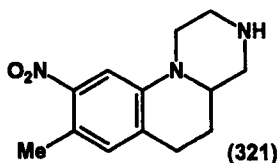
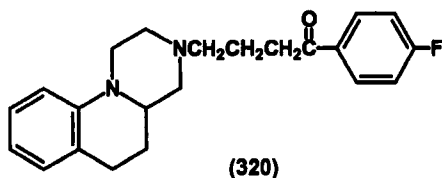
8(9)-(Aroylamido)perhydropyrido[2,1-*c*][1,4]thiazines were investigated as gastric prokinetic agents (92BMC1293). 3,4,6,7-Tetrahydro and 1,3,4,5,6,11*b*-hexahydro[1,4]thiazino[3,4-*a*]isoquinolin-4-ones were patented as antihypertensive agents (81CP1101857), anti-inflammatories (81GEP3023717), and angiotensin I converting enzyme inhibitors (81USP4273927). 3-Methyl-1,3,4,6,11,11*a*-hexahydro[1,4]thiazino[4,3-*b*]isoquinoline-1,4-dione was patented as an antihypertensive agent (87MIP2).

Of the 9-fluoro-10-(cyclicamino)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acids (87JMC465; 88FES1063; 91JHC1061, 91JHC1067, 91MI18; 92MI23; 93JMC3449, 93MI12, 93MI17; 94AAC2651; 96MI8), rifloxacin (**21**) (88MI15; 89MI3) was introduced into human therapy as efficient antibacterial agents against Gram-negative and Gram-positive bacterial infections. The DNA cleavage site specificity of human type II DNA topoisomerase was examined in the presence of the enantiomers of 10-(2,6-dimethyl-4-pyridyl)-9-fluoro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid (95BMC1711; 95MI10, 95MI18).

7,8-Dimethyl-9,10-dihydro-6*H*-pyrido[2,1-*c*][1,4]benzothiazinium bromide was patented as a direct-positive color photographic material and developer [88JAP(K)88/61244].

### C. PYRIDO[1,2-*a*]PYRAZINES AND THEIR BENZO DERIVATIVES

Of the anthelmintic 2-acyl-1,2,3,5,6,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones, the orally effective 1-cyclohexylcarbonyl derivative, praziquantel (**24**), exhibits a broad spectrum with excellent activity against schistosomes and cestodes, and it is widely used in human and veterinary therapy [77E1036; 78H(11)521; 83MI2; 90KFZ(9)60].



*cis*-7,11*b*-H-Aryl-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinolines exhibit atypical antidepressant activities (84JMC995). (7*S*,9*S*)-2-(2-Pyrimidyl)-7-(succinimidomethyl)perhydropyrido[1,2-*a*]pyrazine was patented as a component of synergistic anxiolytic combinations (92USP5124346). Among 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines, the 3-[3-(4-fluorobenzoyl)propyl] derivative exhibits antihypertensive and CNS depressant properties [70JMC516; 72MI2; 80IJC(B)879]. The pharmacological profile of centpyraquin (**320**) was intensively studied (73E1529; 78AF1087, 78AF1092, 78AF1403, 78AF1641). 6-Dipropylamino-3,5,6,7-tetrahydro- and 1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxalinones are potent dopamine D<sub>2</sub> agonists (92JMC1076; 93JMC1301, 93MI21). Other 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines, e.g., **304**, exhibited schistosomacidal activity (72JMC351; 74MI1; 76MI1). Among others, 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines were used to identify and characterize serotonin receptors (91MI9, 91MI10; 93MI13; 94MI10). The affinity of 8-chloro-3-(4-pivaloylaminobutyl)-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline for dopamine D<sub>2</sub> and D<sub>4</sub> receptors was determined (96BMC1227). 9-Bromo- and 9-chloro-1,2,3,5,6,7-hexahydropyrido[1,2,3-*de*]quinoxaline-2,3-diones (94JMC3956; 95BMC1527, 95BMC1533) are investigated as potent antagonists for the glycine binding site of the NMDA receptor. The MAO-A inhibitory activity of 5,6-dimethoxy-1*H*-pyrido[1,2,3-*de*]quinoxaline was investigated [90KFZ(7)15].

Verruculotoxin (**23**) is produced by fungus *Penicillium verruculosum* Peyronel (75MI2; 87MI3). Several synthetic routes were elaborated for its total synthesis (76JA246; 88S963). Verruculotoxin (**23**) and its *p*-fluoro and *p*-methoxy derivatives potentiated twitch tension in skeletal muscle (78MI1). A 2-methyl-1,2,3,4-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinolin-4-one was used as an intermediate in the total synthesis of (±)-quinocarcamide (95JOC6791).

3,8,10-Trimethyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline was claimed for use in photographic materials for the prevention of fading [88JAP(K)88/149643].

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# The Literature of Heterocyclic Chemistry, Part V

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I. Introduction . . . . .	292
II. General Sources and Topics . . . . .	292
A. General Books and Reviews. . . . .	292
B. General Topics by Reaction Type . . . . .	294
C. Specialized Heterocycles. . . . .	304
D. Natural and Synthetic Biologically Active Heterocycles . . . . .	308
III. Three-Membered Rings . . . . .	316
A. General Topics . . . . .	316
B. One Heteroatom . . . . .	316
C. Two Heteroatoms . . . . .	317
D. Three Heteroatoms . . . . .	317
IV. Four-Membered Rings. . . . .	318
A. General Topics . . . . .	318
B. One Heteroatom . . . . .	318
C. Two Heteroatoms . . . . .	318
V. Five-Membered Rings . . . . .	319
A. General Topics . . . . .	319
B. One Heteroatom . . . . .	319
C. Two Heteroatoms . . . . .	324
D. Three Heteroatoms . . . . .	327
E. Four Heteroatoms . . . . .	328
VI. Six-Membered Rings . . . . .	329
A. General . . . . .	329
B. One Heteroatom . . . . .	329
C. Two Heteroatoms . . . . .	333
D. Three Heteroatoms . . . . .	336
E. Four Heteroatoms . . . . .	337
VII. Rings with More Than Six Members . . . . .	337
A. Seven-Membered Rings . . . . .	337
B. Medium Rings . . . . .	338
C. Large Rings . . . . .	339
VIII. Heterocycles Containing Unusual Heteroatoms . . . . .	340
A. Group V Element Heterocycles . . . . .	340
B. Boron Heterocycles. . . . .	342
C. Silicon, Germanium, Tin, and Lead Heterocycles . . . . .	343
D. Selenium and Tellurium Heterocycles . . . . .	344
E. Other Unusual Heterocycles . . . . .	344
References . . . . .	345

## I. Introduction

This survey is a sequel to four already published in *Advances in Heterocyclic Chemistry* [66AHC(7)225; 79AHC(25)303; 88AHC(44)269; 92AHC(55)31]. It includes monographs and reviews published during the period 1991–1993 as well as some published earlier but omitted in Part IV.

Like Parts III and IV, this survey is based mainly on short bibliographic papers published by the authors in *Khimiya Geterotsiklicheskikh Soedinenii* since 1992 (92KGS861; 93KGS273, 93KGS426, 93KGS567, 93KGS849, 93KGS1702; 94KGS280, 94KGS851, 94KGS999; 95KGS276, 95KGS426, 95KGS1421; 96KGS277, 96KGS567, 96KGS1290; 97KGS278). Sources not only in English but also in Russian, German, Japanese, Chinese, French, Czech, Polish, and other languages are surveyed and classified. This feature of the survey should cause no problem because some of the sources are available in English translations and practically all others have informative English abstracts as well as quite understandable and useful schemes and lists of references. As before, carbohydrates are not covered. Such compounds are mentioned only in general cases (e.g., anomeric effect) as well as when carbohydrates serve as starting compounds for the synthesis of other heterocycles or they are present as fragments of a complex system including another heterocyclic moiety such as nucleosides.

## II. General Sources and Topics

### A. GENERAL BOOKS AND REVIEWS

#### 1. *Textbooks and Handbooks*

88M17; 92MI28.

#### 2. *Annual Reports*

a. *Comprehensive Reports.* 90AR(B)189; 91AR(B)197; 92AR(B)167.

b. *Specialized Reports.* Diazines and their benzo derivatives: 89PHC243; 90PHC185; 91PHC205; 92PHC186; 93PHC220.

Five-membered heterocycles with more than one N atom: 89PHC143; 90PHC102; 91PHC124; 92PHC107; 93PHC143.

Five-membered heterocycles with N and S (Se) atoms: 89PHC164; 90PHC118; 91PHC139; 92PHC123; 93PHC159.

Five-membered heterocycles with O and N atoms: 89PHC186; 90PHC146; 91PHC166; 92PHC150; 93PHC185.

Five-membered heterocycles with O and S (Se, Te) atoms: 89PHC178; 90PHC134; 91PHC156; 92PHC7-1138; 93PHC173.

Four-membered heterocycles: 89PHC98; 90PHC37; 91PHC58; 92PHC49; 93PHC69.

Furan and its benzo derivatives: 89PHC126; 90PHC87; 91PHC109; 92PHC95; 93PHC140.

Heterocycles with 8-membered and larger rings: 89PHC317; 90PHC277; 91PHC319; 92PHC279; 93PHC322.

B-Heterocycles and reactions of boranes with heterocycles: 93JOM(457)1, 93JOM(457)25.

Fe-Heterocycles and iron complexes with heterocyclic ligands: 93JOM(457)63. Ruthenium and osmium complexes with heterocyclic ligands, clusters including Ru- and Os-heterocyclic fragments: 93JOM(457)121.

Progress in the total synthesis of natural compounds: 89GSM(11)612; 90GSM(12)486; 91GSM(13)430; 92GSM(14)411; 93GSM(15)356.

Pyridine and its benzo derivatives: 89PHC214; 90PHC166; 91PHC186; 92PHC168; 93PHC202.

Pyrrole and its benzo derivatives: 89PHC111; 90PHC70; 91PHC90; 92PHC81; 93PHC110.

Seven-membered heterocycles: 89PHC297; 90PHC252; 91PHC276; 92PHC253; 93PHC290.

Six-membered heterocycles with O and/or S atoms: 89PHC280; 90PHC229; 91PHC252; 92PHC226; 93PHC264.

Synthesis of heterocycles: 90MI16.

Synthesis of saturated heterocycles: 89GSM(11)547; 90GSM(12)423; 91GSM(13)372; 92GSM(14)363; 93GSM(15)301.

Thiophenes, selenophenes, and tellurophenes: 90PHC50; 91PHC70; 92PHC62; 93PHC82.

Three-membered heterocycles: 89PHC82; 90PHC22; 91PHC42; 92PHC34; 93PHC67.

Transition metal-mediated heterocyclizations and transformations of heterocycles: 93JOM(457)167, 93JOM(457)273.

Triazines, tetrazines, and fused polyaza systems: 89PHC263; 90PHC203; 91PHC223; 92PHC204; 93PHC239.

### 3. *Other Reviews*

Concept of aromaticity in heterocyclic chemistry: 93AHC(56)303. Heteroaromaticity: 91H(32)127.

#### 4. *History of Heterocyclic Chemistry, Biographies*

Chemical research of drugs by the Prof. M. Protiva group: 91CCC2501.

Contribution of Prof. M. Hamana to the chemistry of heteroaromatic *N*-oxides: 92H(33)1.

Eminent chemists of the world. Short biographies: 91MI3.

Investigations in the field of heterocyclic chemistry at Perm University: 92MI42.

#### 5. *Bibliography of Monographs and Reviews*

a. *Comprehensive Data.* Literature of heterocyclic chemistry: 92AHC(55)31.

b. *Specialized Surveys.* 92KGS861; 93KGS273, 93KGS426, 93KGS567, 93KGS849, 93KGS1702; 94KGS280, 94KGS851, 94KGS999; 95KGS276, 95KGS426, 95KGS1421; 96KGS277, 96KGS567, 96KGS1290; 97KGS278.

### B. GENERAL TOPICS BY REACTION TYPE

#### 1. *Structure and Stereochemistry*

a. *Theoretical Aspects.* Electron and proton transfer in heterocyclic chemistry: 92MI148, 92MI149.

Formation and transformation of heterocycles in the solid state: 93SL303.

Hetarynes, formation and reactions in gas phase: 93SL9.

Heterocycles as fragments of supramolecular assemblies: 93MI9.

Heterocyclic radical cations, structure: 92MI16.

Hydrogen bonds, ion pairs, and host-guest interactions in heterocycles: 91MI38.

Molecular design of heterocycles: 92KGS808; 93KGS1299.

Prototropic tautomerism of heteroaromatic compounds: 91H(32)329.

Relation between type and order of bonds and their lengths, estimation of heteroaromaticity: 91H(32)2023.

Rotation isomerism of *trans*-1-aryl-2-hetaryl- and -dihetarylethylenes: 91CRV1679.

Theoretical and industrial importance of heterocyclic chemistry: 92KGS291.

b. *Molecular Dimensions.* Structure peculiarities of metal complexes with heterocyclic  $\beta$ -aminovinylimines and formazanes as ligands: 91KK1011.

X-ray data for coordination compounds of metals with anion ligands based on nitroxyl radicals, derivatives of imidazoline, piperidine, pyrrolidine, and pyrroline: 93ZSK119.

c. *Molecular Spectra.*  $^{13}\text{C}$ – $^{13}\text{C}$  Coupling constants through more than one bond in heterocycles: 91MI48.

Heterocyclic radicals and radical ions, ESR spectra of solutions: 88MI3.

Heterocyclic analogs of 9,10-dihydroanthracene, mass spectrometry of: 91UK982.

d. *Stereochemical Aspects.* Chiral N-heterocycles as ligands promoting enantioselective addition of organometallic reagents to carbonyl compounds: 91AG(E)49.

Conformational analysis of saturated fused 1,3-heterocycles: 92ACH107.

Heterocycles as ligands in metal complexes for organized fluid phases: 91AG(E)375.

Medium effect on thermodynamic parameters of conformational conversions in some 6- to 8-membered O-, S-, and O,S-heterocycles: 93ZOB721.

Molecular assemblies and helices containing 2,2'-bipyridine fragments: 91AG(E)1450.

e. *Betaines and Other Unusual Structures.* N-(Oxidophenyl)pyridinium betaine dyes: 92CSR147.

f. *Miscellaneous Substituted Heterocycles.* Acetylenic  $\alpha$ - and  $\beta$ -amino acids possessing heterocyclic fragments: 91UK1318.

Carbohydrate-based asymmetric synthesis of  $\alpha$ -amino acids having heterocyclic fragments: 91T6079.

Chiral heterocycles as reagents for NMR determination of enantiomeric purity: 91CRV1441.

N-Dienyl lactams, preparation and Diels–Alder reactions: 90OPP315.

Divinyldisulfides with heterocyclic substituents: 92MI17.

Double calixarenes containing O- and S-heterocyclic fragments: 93SL719.

Esters of hetaryl-substituted  $\alpha$ -oxo and  $\alpha$ -hydroxy acids: 90MI10.

Fluorinated heterocycles: 93AHC(59)1, 93MI2.

Formazanes, derivatives of heterocyclic carboxylic acids: 92MI12.

Hetarylferrocenes: 91KGS147.

Heteroaromatic carbenes: 92KGS1155.

Heterocycles fused with cyclobutadiene: 92CRV1685.

Isothiocyanates, derivatives of heterocycles: 91CRV1.

Phosphazenes containing heterocyclic fragments: 91OPP1.

Polycyclic cage heterocycles as intermediates in organic synthesis: 91SL43.

Propargyl derivatives of heterocycles: 93MI4.

Saturated fused 1,3-heterocycles: 92ACH107.

Synthesis, structure, and reactions of heterocyclic *N*-oxides and *N*-imides: 92H(33)1011.

Trihalomethylcarbinols possessing heterocyclic residues: 91UK2543.

Troponoids fused with heterocycles: 92MI30.

## 2. Reactivity

a. *General Topics.* Biotransformations of heterocycles: 91MI53; 92MI26.  
Chemistry of heteroaromatic hydroxy-, mercapto-, and selenoaldehydes: 92KGS5.

Chlorosulfonylation of heteroaromatic systems: 91PS(56)245.

Cleavage of O–O, S–S, N–O, N–S, and N–N bonds in heterocycles with their participation as nucleophiles on thermolysis, photolysis as well as in charge-transfer processes: 91G461.

Donor–acceptor concept and reactivity of heteroaromatic compounds: 92H(33)1129.

Electrochemical chlorination, bromination, and iodination of heterocycles: 90M120.

Electrochemical fluorination of heterocycles: 90MI21.

Enantioselective addition of organozinc reagents to heterocyclic aldehydes: 92CRV833.

Glycosylation of natural heterocycles: 93CRV1503.

Hetaryl-substituted perfluoroalkyl(aryl)acetylenes, reactions with heterocycles: 91UK1005.

Heterocycles as intermediates in the synthesis and fragments of molecular knots: 92NJC277.

N,S- and N,O,S-Heterocycles as precursors of N<sub>2</sub>S, thiofulminic acid, and nitrile sulfides: 91CRV363.

Heterocycles in synthesis of taxane diterpenes: 92YGK554.

Heterocycles in total synthesis of fused tricyclic terpenoids: 92YGK563.

Heterocyclic radical cations, reactivity: 92MI16.

Heterocyclic fragments as auxiliaries in stereochemically controlled radical reactions: 91ACR296.

Ligand coupling reactions of heterocycles having hypervalent side-chain or ring S, P or metal atoms: 91ACR202.

Mass spectrometry of halogenated heterocycles: 91UK2143.

Mn(III)-mediated transformations of heterocycles: 93S833.

Nitroenamines in transformations of heterocycles: 93KFZ(4)41.

Perspectives on large-scale transformations of optically active heterocycles: 91T4789.



Photochromic reactions with the formation or transformation of heterocycles: 90MI15.

Polyfunctional organozinc reagents in transformations of heterocycles: 93CRV2117.

Polymerization of O-, N-, and N,O-heterocycles: 91RTC526.

Properties, uses, and biological role of heterocycles: 93MI7.

Pummerer reaction in transformations of heterocycles: 91UK1255.

Reactions of  $\alpha$ -chlorosulfides with heterocycles in synthesis of natural products: 92YZ215.

Reactions of fluorinated ketimines with heterocycles: 92UK1457.

Reactions of hetarenes coordinated with transition metals: 93AHC(58)123.

Reactions of heterocycles at high pressures: 91MI18.

Reactions of N- and O-heterocycles in aqueous media: 93CRV2023.

Ring-ring tautomerism in 5- and 6-membered heterocycles: 92KGS851.

Transformations of heterocycles induced by baker's yeast: 91CRV49.

Transformation of heterocycles on Rh(II)-mediated reactions of diazo-carbonyl compounds: 91T1765.

Transformations and synthesis of heterocycles under conditions of Kolbe electrolysis: 90MI24.

Transformations of heterocycles with participation of tellurium compounds: 91S793, 91S897.

Trifluoromethanesulfonyl chloride in transformations of heterocycles: 91UK1645.

Trifluoromethylation of heterocycles: 91Y GK612.

Unsaturated heterocycles in asymmetric conjugated addition reactions: 92CRV771.

Use of heterocycles in synthesis of  $\beta$ -oxygenated  $\gamma$ -amino acids and  $\gamma$ -oxygenated  $\delta$ -amino acids from  $\alpha$ -amino acids: 92H(33)1051.

Use of high pressure in heterocyclic chemistry: 91T8463.

b. *Reactions with Electrophiles and Oxidants.* Conjugated halogenation of heterocycles: 93S1177.

Halogenation of heterocycles fused with other aromatic or heteroaromatic rings: 93AHC(59)245.

Halogenation of 6- and 7-membered heterocycles: 93AHC(58)271.

Mechanisms and rates of electrophilic hydrogen isotope exchange and nitration in heterocyclic series: 92H(34)2179.

Nitration of phenyl-substituted heterocycles: 93AHC(58)215.

Reactions of heterocycles with  $\alpha$ -chlorosulfides leading to C-C bond formation: 93YZ215.

Selective fluorination of heteroaromatic compounds: 92CRV505.  
Trifluoromethylation of heterocycles: 92T6555.

c. *Reactions with Nucleophiles and Reducing Agents.* Pd-Catalyzed reactions of organotin compounds with heterocycles: 92S803.

Enzymatic reduction of nitro compounds of heterocycles: 90MI18.

Lithiation of heterocycles directed by  $\alpha$ -aminoalkoxides: 92SL615.

Nucleophilic reactions of hetarylsilanes and hetarylgermanes: 93KGS869.

Radical chain nucleophilic substitution of heterocycles: 91MI39.

Reactions of heterocycles with organocopper reagents: 92SL769.

Vicarious nucleophilic substitution of hydrogen in heterocyclic chemistry: 91S103; 93MI25.

d. *Reactions Toward Free Radicals, Carbenes, etc.* Catalytic cyclopropanation of heterocycles by diazomethane: 93UK847.

Cyclic nitroxyl radicals as spin traps for inorganic radicals: 91CSR341.

Reactions of cyclic peptides, nucleic acids, and pyrimidine bases with peroxy radicals in aqueous solutions: 91AG(E)1229.

Reactions of heteroaromatics with diazoesters: 92MI3.

Reactions of heterocycles with alkoxy-carbonyl-carbenes: 93UK485.

Reactions of N-, O-, and S-heterocycles with carbenes and carbenoids to form ylides: 91CRV263.

Reactions of radical cations formed from saturated N-heterocycles by photoinduced electron transfer: 92SL546.

Selectivity in radical transformations of heterocycles: 93CSR143.

e. *Reactions with the Cyclic Transition State.* Pericyclic reactions in transformations of heterocycles to other heterocycles or carbocycles: 92BSB521.

Reactions of heterocycles with nitrile imines and their precursors: 93CRV2731.

Retroene reactions with participation of heterocycles: 93S659.

f. *Reactivity of Substituents.* Photoinitiated processes in heterocyclic azomethines: 92MI10.

Reactions of organozinc derivatives of hetarenes catalyzed by transition metals: 92T9577.

g. *Heterocycles as Intermediates in Organic Synthesis.* Amino acids containing heterocyclic fragments as chiral building blocks in organic synthesis: 91AG(E)1531.

Biphosphinic ligands containing pyrrolidine and 1,3-dioxolane fragments in highly efficient Rh catalysts for asymmetric hydrogenation: 92SL169.

Heterocycles as intermediates in synthesis of fluorine-containing aliphatic amino acids: 91UK1680.

Heterocycles as precursors of carbenes and ketenes, including those with heterocyclic fragments, in gas phase: 93SL9.

Heterocycles in synthesis of divinyldisulfides: 92MI17.

Heterocyclic anions in electroorganic synthesis: 93T9627.

Oxazolones in synthesis of fluorine-containing aromatic amino acids: 91UK2047.

Transformations of heterocycles containing an ONO fragment: 93CRV725.

### 3. *Synthesis*

a. *General Topics.* Acylium salts in syntheses of heterocycles: 90OPP1.

Alkoxy-carbonyl-carbenes in synthesis of heterocycles: 93UK485.

Amide and lactam acetals in synthesis of heterocyclic compounds: 92KGS762.

Amino derivatives of  $\alpha,\beta$ -unsaturated carbonyl compounds of ethylenes and acetylenes in the synthesis of heterocycles: 92KGS867.

Aminomethylenemalonates and their use in heterocyclic synthesis: 92AHC(54)1.

Asymmetric synthesis and separation of heterocycles: 93CRV2037.

Asymmetric synthesis of hetero- $\alpha$ -amino acids: 92CRV889.

Ni- And Pd-catalyzed formation of the C-C bond in heterocycles: 92S413.

Cations and radicals in heterocyclic synthesis: 92JHC653.

Chiral Lewis acids as catalysts in hetero-Diels-Alder and in [2 + 2]-cycloaddition reactions leading to heterocycles: 91S1.

Dianions in synthesis of heterocycles: 91T4223.

Formation of cyclic peroxides by photooxygenation of olefins: 93CSR59.

Formation of lactones under transesterification conditions: 93CRV1449.

Formation of N- and O-heterocycles in aqueous media: 93CRV2023.

Haloalkyl isothiocyanates as versatile reagents in heterocyclic chemistry: 92H(33)973.

Industrial syntheses of optically active heterocycles: 93MI14.

Mn(III)-mediated syntheses of heterocycles: 93S833.

Nitroenamines in synthesis of heterocycles: 93KFZ(4)41.

Organometallic carboxamidation in synthesis of heterocycles: 90OPP269.

Perspectives of large-scale synthesis of optically active heterocycles: 91T4789.

Polyfunctional organozinc reagents in synthesis of heterocycles: 93CRV2117.

Proteins, enzymes, and bacteria cells in synthesis and biotransformations of heterocycles: 89PHC65.

Radical chain nucleophilic substitution in synthesis of heterocycles: 91MI39.

Reactions of fluorinated ketimines to give heterocycles: 92UK1457.

Regio- and enantioselective synthesis of heterocycles using organometallic catalysts: 92PAC315.

Selective syntheses of heterocycles: 91AG(E)477.

Selectivity in radical heterocyclizations: 93CSR143.

Stereoelectronic effects in the formation of 5- and -6-membered heterocycles: 93ACR476.

Syntheses and transformations of heterocycles in reactions of carbonyl compounds with Vilsmeier reagents: 92T3659.

Syntheses of heterocycles by intramolecular reactions of carbenoids: 92T5385.

Syntheses of heterocycles using thio-, seleno-, and telluroaldehydes, and thio- and selenonitroso compounds as heterodienophiles: 92AHC(55)1.

Syntheses of heterocyclic systems with participation of iron compounds: 92SL371.

Synthesis of fused heterocycles, general monograph: 87CH(47), 92CH(47,2)1.

Synthesis of heterocycles, particularly alkaloids, using cationic cyclizations: 92ACR352.

Synthesis of heterocycles using the Diels–Alder reaction with inverse electron demand: 89PHC30.

Synthesis of heterocycles with participation of vinyl phosphonates: 92S333.

Synthesis of juvenyl hormones and juvenoids possessing heterocyclic fragments: 92UK1332.

Synthesis of N- and O-heterocycles, *peri*-fused naphthacenequinone derivatives: 93UK1078.

Synthesis of saturated 5-membered heterocycles using organosilicon compounds: 92YZ147.

Synthesis of tricyclic compounds containing a 4- to 7-membered heterocycle *peri*-annulated to a naphthalene system: 90AHC(51)1.

Uracyls as versatile starting compounds in heterocyclic synthesis: 92AHC(55)129.

Use of microwave emission in the synthesis of heterocycles: 93CLY627.

Use of synthons in heterocyclic chemistry: 93MI13.

b. *Ring Synthesis from Nonheterocyclic Compounds.* Aromatic N-oxides as 1,3-dipoles in reactions with unsaturated compounds: 92KGS579. •

Aryl- and alkylsilylthioketones and synthetic equivalents of thioaldehydes in cycloaddition reactions with 1,3-dipoles, dienes, and heterodienes: 93PS(74)31.

Asymmetric cycloaddition reactions with amino acid esters as chiral auxiliaries: 91G227.

Cycloaddition of nitrile oxides to multiple bonds containing heteroatoms: 93UK1164.

Cycloaddition reactions of acylketenes to give heterocycles: 92MI43.

Cycloaddition reactions of norbornadiene and its derivatives to give heterocyclic systems: 92MI25.

$\beta$ -Enaminonitriles as versatile reagents in synthesis of heterocycles: 93CRV1991

Formation of heterocycles on Rh(II)-mediated reactions of diazocarbonyl compounds: 91T1765.

Formation of heterocycles by nucleophilic substitution of aliphatic nitro groups: 91S423.

Formation of O- and N-heterocycles by Pd-catalyzed intramolecular 1,4-addition reactions of conjugated dienes: 92PAC429.

Formazanes in synthesis of heterocycles: 92MI12.

Free-radical intramolecular cyclization in synthesis of heterocycles: 93KGS1011.

Heterocyclization of aliphatic trichloromethyl-substituted compounds: 93KGS980.

Heterocyclization of enamines: 90MI2.

Heterocyclizations of propargyl compounds: 93MI4.

Heterocyclizations using C-H bond activation by transition metals: 92PAC335.

Hetero-substituted nitroalkenes in the synthesis of heterocycles: 91CSR95.

Hydroxylamine-*O*-sulfonic acid in the synthesis of heterocycles: 90WCH243.

Intramolecular radical heterocyclizations: 91ACR139.

Intramolecular  $S_N$  heterocyclizations: 92T7383.

Methyl 2-benzoylamino-3-dimethylpropenoate in the synthesis of heterocycles: 93PHC34.

Methylenemalononic aldehydes in the synthesis of heterocycles: 91KGS1011.

Nickel-mediated intramolecular cyclizations of enynes, dienynes, bisdienes and diynes leading to heterocycles: 92SL539.

Nucleophilic reactions of quinones resulting in heterocyclization: 91T8042.

Preparation of heterocycles by 1,3-dipolar cycloaddition of diazoesters: 92MI3.

Pummerer reaction in synthesis of heterocycles: 91UK1255.

Silylated azomethyne ylides and thiocarbonyl ylides in synthesis of heterocycles: 92YGK48.

Syntheses of heterocycles using the aza Wittig reaction: 91UK285.

Syntheses of heterocycles with participation of chlorocarbonyl isocyanate: 93T3227.

Syntheses of trifluoromethyl-substituted heterocycles from open-chain compounds: 91YGK612.

Synthesis of heterocycles based on isothiocyanates: 91CRV1.

Synthesis of heterocycles based on malononitrile: 91MI6.

Syntheses of heterocycles based on trichloroacetonitrile: 93KGS1443.

Synthesis of heterocycles from  $p,\pi$ -unsaturated amines and bifunctional reagents: 91UK103.

Transformations of trihalomethylcarbinols to heterocycles: 91UK2543.

c. *Syntheses by Transformation of Heterocycles.* Functionalization of heterocycles via Ni- and Pd-catalyzed reactions: 91UK339.

Heteroaromatic cations as key intermediates in synthesis of functionalized dihydroheteroaromatics: 92BSB339.

Synthesis of heterocycles by intramolecular radical reactions of carbohydrate derivatives: 92MI18.

Trithiazyl trichloride in synthesis of 5-membered N,S-heterocycles: 92JHC639.

#### 4. *Properties and Applications (Except Drugs and Pesticides)*

a. *Dyes and Intermediates.* Heterocycles as dyes for optical discs: 92UK102.

N-(Oxidophenyl)pyridinium betaine dyes: 92CSR147.

Polymethine dyes, derivatives of N-, O-, S-, and N,S-heterocycles: 91UK1708.

b. *Substances with Luminescent and Related Properties.* Heterocycles with photochromic properties: 91YGK373, 91YGK554.

c. *Organic Conductors (Except Polymers).* Conducting charge-transfer salts based on thiophene and thienothiophene analogs of tetracyanoquinodimethane and on bis-ethyldithiotetrathiafulvalene and its Se and Te analogs: 91CSR355.

d. *Coordination Compounds.* Binaphthyl chiral auxiliaries with heterocyclic fragments as substituents or part of a fused system: 92S503.

Chromatographic determination of metals as chelates with heterocyclic azo compounds: 93ZAK1094.

Heterocycles as ligands in catalysts for alkane activation: 92MI2.

N-,S-, and N,S-Heterocycles as extragents: 93MI5.

e. *Polymers.* Conductive poly(thiophene) as a chemically modified electrode: 93WCH299.

Electron-conductive polymers, poly(pyrroles), poly(thiophenes), poly(furan), poly(quinoline), and poly(benzo[c]thiophene): 90MI22; 91MI56.

B-Heterocycles in the synthesis of organometallic polymers: 91UK1553.

Metal-chelate monomers with 5- and 6-membered heterocyclic fragments: 91UK1532.

Preparation of polymers using an addition reaction of epoxides with esters: 91Y GK218.

Polycyclization reactions to give polymers possessing heterocyclic fragments: 92UK1864.

Polyheteroarylenes based on bis-naphthalic anhydrides: 92UK815.

Polymers based on vinylacetylenic piperidine derivatives: 91MI2.

Polymers containing heterocyclic fragments: 91UK1449.

Poly(pyrrole) as a base of electrocatalytic materials: 91CSR391.

Saturated N-, O-, and N,O-containing bis-heterocycles in synthesis of polymers: 92UK161.

Synthesis, properties, and uses of poly(pyrrole) and its composites: 91CLY794.

Synthesis, functionalization, and uses of conjugated poly(thiophenes): 92CRV711.

Thermostable polymers containing heterocyclic fragments: 91RTC481.

f. *Miscellaneous.* Chiral heterocycles as catalysts for asymmetric Diels–Alder reactions: 92MI41.

Chiral heterocycles as ligands and auxiliaries for enantioselective catalysts: 92CRV935.

Fulgides and spiropyranes as materials able to reversible photocyclization–decyclization, allowing storage of optical data: 93T8267.

Heterocycles and their complexes used for modification of electrodes: 90MI23.

Heterocycles as materials for irreversible thermooptic memory systems: 91CLY1090.

Heterocycles as solvents: 91MI8.

N-Heterocycles as ligands in complex catalysts for selective functionalization of saturated hydrocarbons: 92ACR504.

S-Heterocycles and derivatives of heterocycles with sulfur-containing substituents having industrial importance: 93PS(74)173.

Heterocyclic azo compounds in analytical chemistry: 91ZAK645.

Macroheterocycles and heterocyclic cage compounds as  $\pi$ -donors: 92BSB555.

Photochromic fulgides: 91YGK364.

Photoindicators for photomemory systems of initiated free radicals: 93CRV435.

Polymer-immobilized complexes with heterocyclic ligands as catalysts: 92UK257.

Ruthenium oxo complexes with N-heterocyclic ligands as organic oxidants: 92CSR179.

### C. SPECIALIZED HETEROCYCLES

#### 1. Nitrogen Heterocycles (*Except Alkaloids*)

a. *General Sources and Topics.* Chemistry of unsaturated N-heterocycles possessing carbonyl groups: 93AHC(58)171.

Electric moments of some N-heterocycles from X-ray difraction data: 92CRV1769.

Heterocyclic nitroxyl radicals as spin tracers in studies of biological membranes: 88MI4.

Host-guest complexes of azaaromatic quaternary salts: 93H(36)1645.

Hydrofluorides of N-heterocycles: 91T5329.

Peculiarities of retention of N-heterocycles in liquid chromatography: 92MI50.

Polycyclic N-heteroaromatic cations: 92AHC(55)261.

Sulfoxides and sulfines, derivatives of N-heterocycles: 91PS(58)129.

Ylides, derivatives of saturated N-heterocycles: 91AKZ25.

b. *Structure and Stereochemistry.* Conformations of 5- and 6-membered cyclic nitroxyl radicals, study by ESR spectra: 88MI6.

N-Heterocycles as ligands in ruthenium clusters: 91POL277.

Paramagnetic metal complexes with heterocyclic nitroxyl radicals as ligands: 89MI2.

Stereochemistry of metal complexes with N-heterocycles as ligands: 91MI61.

Transition metal complexes with N-heterocycles as ligands possessing coordination node  $MN_4$ : 91MI36.



c. *Reactivity.*  $\alpha$ -Amino azaheterocycles, condensation with  $\beta$ -keto-esters: 91UK2172.

Chiral formamidines, derivatives of N-heterocycles in asymmetric synthesis: 92T2589.

Cyclic enamines, reactions with halocarbenes: 90MI4.

N-Fluorolactams as fluorinating agents: 92YGK338.

Generation and reactions of  $sp^2$  carbanionic centers vicinal to heterocyclic N atoms: 93AHC(56)155.

Hydrodenitrogenation: 91IEC2021.

Mechanism of C-methylation in natural N-heterocycles: 93PS(74)59.

New strategies in lithiation of N-heterocycles: 89PHC1.

Radical reactions of protonated N-heteroaromatic compounds: 93G9.

Ring-chain tautomerism of nitrogen-containing derivatives of  $\beta$ -dicarbonyl compounds: 90MI8.

d. *Synthesis.* Aminocarbene complexes of Cr and Mo as initiators in cascade reactions of amines leading to novel heterocyclic compounds via nitrogen ylides: 91CSR503.

Asymmetric synthesis of bioactive N-heterocycles using intramolecular olefin aminocyclization with secondary allyl alcohols: 93YZ229.

Azabutadi-1,3-enes in the synthesis of 6-membered N-heterocycles: 92KGS1299.

Pd-Catalyzed intramolecular amination of olefins leading to N-heterocycles: 91MI40.

Cyclic enamines, derivatives of nitroxyl radicals: 90MI3.

Formation of N-heterocycles by insertion of molecular  $N_2$ : 91YGK937.

Formation of N-heterocycles from phosphorus-containing diazo compounds: 92UK564.

N-Heterocycles, formation from O-nitrenes: 91MI10.

N-Heterocycles, formation in Diels-Alder, 1,3-dipolar, and [2 + 2]-cycloaddition reactions: 90MI13.

Immonium ylides from halocarbenes in the synthesis of N-heterocycles: 93IZV646.

Intramolecular Michael and anti-Michael addition at the triple carbon-carbon bond in the synthesis of N-heterocycles: 93SL369.

New synthesis of N-heterocycles on rearrangement of spiro-5-isoxazolines: 93SL1.

Preparation of diazoesters from N-heterocycles: 92MI3.

Preparation of nitrogen polycyclic compounds using organotin reagents: 91YGK128.

Synthesis of coumestans and azacoumestans: 93H(35)1425.

Synthesis of heterocycles from azadienes: 93AHC(57)1.

Synthesis of N-heterocycles from (vinylimino)phosphoranes and related compounds: 93MI21.

Synthesis of N-heterocycles with participation of carbene complexes: 91SL381.

Synthesis of lactams by reactions of primary and secondary enamines with electrophilic olefins: 90MI6.

Synthesis of saturated N- and N,O-heterocycles by addition of nitrogen-containing reagents to alkenylsilanes: 92MI38.

## 2. Oxygen Heterocycles

a. *Chemistry of Individual Classes of O-Heterocycles.* New cyclic 5-membered carbon oxides and oxidosulfides, fullerene oxides: 93PS(74)295.

b. *Reactivity.* Furan and bridged O-heterocycles in synthesis of cyclacenes: 92CSR215.

Heterocycles with several O atoms as oxidants: 93MI8.

Hydrodeoxygenation: 91IEC2021.

Oxidation of cyclic acetals: 92MI9.

Reactions of O-heterocycles involving carbonyl oxides: 91CRV335.

Ring-opening reactions in oxabicyclic systems as a route to cyclic and acyclic compounds with several stereocenters: 93SL177.

Stereoselective syntheses of unusual amino acids using formation of epoxides and cyclic carbamates, and halolactonization as key steps: 92ACR360.

c. *Synthesis.* Aryl synthons in the synthesis of natural polycyclic O-heterocycles: 91SL134.

Asymmetric catalysis of carbonyl- $\alpha$ -enone reactions leading to chiral O-heterocycles: 92SL255.

Bicyclic ketals in stereocontrolled synthesis of 6 to 8-membered saturated O-heterocycles: 92SL97.

Carbonyl ylides in the synthesis of O-heterocycles: 91ACR22.

[2+2]-Cycloaddition reactions with polyfluoroketones to give O-heterocycles: 92UK1422.

Formation of O-heterocycles with participation of carbonyl oxides: 91CRV335.

O-Heterocycles, formation in Diels-Alder, 1,3-dipolar, and [2+2]-cycloaddition reactions: 90MI13.

Ni(II)/Cr(II)-Mediated coupling reactions in synthesis of natural saturated O-heterocycles: 92PAC343.

Synthesis of bioactive sesquiterpene lactones: 92YGK858.

Synthesis of complex natural O-heterocycles: 91AG(E)455.

Synthesis of O-heterocycles using Pd(II) catalysts: 92H(33)1079.

Synthesis of quinone derivatives containing saturated O-heterocyclic substituents as *S*-lipoxygenase inhibitors and antagonists of thromboxane A<sub>2</sub> receptors: 92YGK786.

### 3. Sulfur Heterocycles

a. *Chemistry of Individual Classes of S-Heterocycles.* Cyclic sulfides and sulfates as synthons similar to epoxides: 92S1035.

Cyclic sulfides as ligands in transition-metal complexes: 91MI20.

Intermediates in the formation of spirothiofuranes: 91PS(58)39.

$\alpha$ -Oxoketene cyclic dithioacetals: 92MI39.

2,4,6,8-Tetrathiaadamantanes: 91UK736.

b. *Structure and Stereochemistry.* Dications, derivatives of S-heterocycles with two heteroatoms: 91YGK636.

New cyclic 4-, 5-, 7-, 8-, and 10-membered carbon sulfides and 5-membered oxidosulfides: 93PS(74)295.

Sulfoxides and sulfines, derivatives of S-heterocycles: 91PS(58)129.

c. *Reactivity.* Cathodic transformations of cyclic and hetaryl sulfones: 93PS(74)93.

Chemical behavior of cyclic polysulfides: 91PS(59)79.

Chiral cyclic sulfates in synthesis of sulfates labeled with <sup>17</sup>O and <sup>18</sup>O: 91PS(59)66.

Chiral cyclic sulfites in asymmetric synthesis of sulfoxides: 91PS(58)89.

Cyclic dithioacetals in organic synthesis: 91ACR257.

Cyclic mono- and dithioacetals in synthesis of sulfones: 91PS(58)207.

Cyclic sulfides and disulfides in syntheses of thioaldehydes and thioketones: 93CSR199.

Desulfurization of cyclic sulfides on metal surfaces and with organometallic complexes: 92CRV493.

Extrusion of SO<sub>2</sub> from heterocycles: 92PHC1; 93PHC1.

*N*-Fluorosultams as fluorinating agents: 92YGK338.

Hydrodesulfurization: 91IEC2021.

Metallocomplex catalysis in transformations of S-heterocycles: 93JOM(455)1.

Reactions of heterocycles with S<sub>2</sub> and those involving elimination of S<sub>2</sub>: 91ACR341.

d. *Synthesis.* Cyclic polysulfides, formation in reactions of cumulenes and 1,2,3-selenadiazoles with sulfur: 91PS(58)179.

Electrochemical activation of sulfur in organic solvents and synthesis of S-heterocycles: 92MI44.

Formation of heterocycles from diatomic sulfur: 91ACR341.

Formation of S-heterocycles on reactions of CS<sub>2</sub> with C-nucleophiles: 91MI52.

Metallocomplex catalysis in the synthesis of S-heterocycles: 93JOM(455)1.

## D. NATURAL AND SYNTHETIC BIOLOGICALLY ACTIVE HETEROCYCLES

### 1. *General Sources and Topics*

Biochemical methods in the enantioselective synthesis of natural products possessing oxirane and lactone fragments: 92BSB393.

Progress in the chemistry of organic natural products: 91FOR(56), 91FOR(57), 91FOR(58); 92FOR(59); 92FOR(60); 93FOR(61), 93FOR(62).

Free-radical processes in tissues and in natural and synthetic bioactive compounds: 88MI5.

Glycols in the enantiospecific synthesis of natural products: 93UK621.

Hydrogen bonding in the structure of bioactive naturally occurring heterocycles: 91MI15.

Oligonucleotide derivatives as gene-directed bioactive compounds: 91MI54.

Quantitative aspects of molecular recognition: 91MI32.

Radical reactions in the syntheses of natural N- and O-heterocycles: 91CRV1237.

Regio- and stereoselective heterocyclizations in syntheses of natural products: 92PAC1883.

Role of heterocycles in cancerogenesis: 90MI19.

Structure and biological activity of Zn(II) complexes with N-heterocyclic ligands: 93WCH327.

Synthetic modifications of natural N- and O-heterocycles: 93SL313.

Vanadium heterocycles and complexes with natural and synthetic heterocycles: 91AG(E)148.

### 2. *Alkaloids*

a. *General.* Alkaloids as specific catalysts in the electrosynthesis of chiral compounds: 91UK2113.

Chemistry and biological action of alkaloids: 89MI5; 90MI25; 91MI25; 92MI46, 92MI47; 93MI10, 93MI11.

HPLC of alkaloids: 91KPS595.

Immune analysis of alkaloids: 93UK831.

b. *Structure.* Stereochemistry of bis-quinolizidine alkaloids of the spartein type: 92H(33)1101.

c. *Synthesis.* Asymmetric synthesis of alkaloids using construction of a pyrrolidine ring by intramolecular aminocyclization of secondary allyl alcohols at the olefin bond: 92YZ229.

Stereoselectivity in synthesis of alkaloids: 92JHC631.

Syntheses of heterocyclic systems with participation of compounds of iron and its use in alkaloid chemistry: 92SL371.

Synthesis of polycyclic alkaloids using an intramolecular double Michael reaction: 93AG(E)1010.

Synthesis of vinblastin and related alkaloids: 93ACR559.

Synthetic approaches to stereoisomers and analogs of indolizidine alkaloid castanospermine: 92T4045.

Thioaldehydes as heterodienophiles in the synthesis of morphine alkaloids: 93PS(74)17.

Total synthesis of (–)-acetomycine: 91YGK327.

Total synthesis of cephalotoxine: 91MI34.

d. *Individual Groups of Alkaloids.* Antitumor alkaloids of elipticine and vinblastine groups: 92CSR113.

Cage alkaloids of *Daphniphyllum macropodum*: 92AG(E)665.

Colchicin and related compounds: 92CLY445.

Cytisine, a quinolizidine alkaloid: 91KPS301.

Dimeric tropane alkaloids: 91KPS447.

Ergot alkaloids, chemistry, biological effects, and biotechnology: 90MI14.

Organometallic compounds in the chemistry of morpholine alkaloids: 91MI42.

Stacking modeling of purine alkaloids: 91MI28.

### 3. Antibiotics

a. *General.* Antibiotics and the bacterial cell membrane: 91MI1.

Synthesis of optically active antibiotics and related compounds: 92SL691.

b. *Antitumor Antibiotics*. Antitumor antibiotics of the enediyne group: 91AG(E)1387; 93MI32.

Calicheamycins, chemistry and mechanism of action: 91ACR235.

Chemistry of mitomycins: 92SL778.

Duocarmycins: 91MI22.

Neocarcynostatine, mechanism of action: 91ACR191.

Syntheses of antitumor enyne antibiotics possessing O-heterocyclic fragments: 92YGK940.

Synthesis of anthracycline antibiotics: 92YGK131.

Total synthesis of antitumor antibiotic neooxazolomycine: 92YGK61.

c.  *$\beta$ -Lactam Antibiotics*. Aztreonam, monocyclic  $\beta$ -lactam antibiotic with aminotriazolyl as a substituent: 92MI31.

Cephmetazole, modified cephem antibiotic bearing tetrazole as substituent: 93MI28.

Classification and properties of penicillins: 93MI27.

Properties and synthesis of  $\alpha,\beta$ -dehydropeptides including penicillin and antibiotics: 91WCH689.

Studies of oxacephems, artificial  $\beta$ -lactam antibiotics: 91YZ77.

d. *Macrocyclic Antibiotics*. Chemistry, biochemistry, and total syntheses of macrolide antibiotics avermectins and milbemycins: 91CSR211, 91CSR271.

Nonpolyenic antifungal macrolide antibiotics: 91MI27.

Preparation, modification, and medical uses of nistatin: 93KFZ(2)14.

Syntheses of rifamycin S and ionomycin using ring opening of oxabicyclic systems: 92AC1873.

Synthesis of erythromycin: 91AG(E)1452.

Total synthesis of aglycone of venturicidines A and B: 90YZ789; 91YGK657.

Total synthesis of KF-506: 91YGK748.

Total synthesis of milbemycin  $\alpha_1$ : 91YGK737.

e. *Miscellaneous Antibiotics*. Enediyne antibiotics containing heterocyclic fragments: 92ACR497; 93PS(74)47.

Lantibiotics: polycyclic peptide antibiotics: 91AG(E)1051.

Properties and synthesis of  $\alpha,\beta$ -dehydropeptides including penicillin and lantibiotics: 91WCH689.

Syntheses of rifamycin S and ionomycin using ring opening of oxabicyclic systems: 92PAC1873.

Synthesis of oxetanocine, a nucleoside antibiotic with anti-HIV action, and of related compounds: 91YGK670.

Synthesis of tetrodotoxin: 92BSB617.

Synthesis of tetrodotoxin and enediyne antibiotics: 92JHC619.

#### 4. *Vitamins*

Analytical control of vitamin B<sub>1</sub> quality: 93KFZ(3)57.

Biosynthesis of vitamin B<sub>12</sub> and its analogs: 91MI31; 93AG(E)1223.

Synthesis of biologically active  $\alpha$ -tocopherol esters: 91MI29.

#### 5. *Drugs*

a. *General.* Chemistry of natural drugs: 92YZ1.

Heterocycles on the world market of drugs: 92MI1.

Metabolism of drugs: 91KFZ(3)6, 91YZ737.

Microbial iron chelators as agents transporting drugs: 93ACR241.

Modification of drugs: 91M155.

Physiologically active complexes based on hydrazones with heterocyclic fragments: 92KFZ(5)30.

Silyl modification of drugs: 93MI30.

Study and development of synthetic bioactive analogs of natural drugs: 92YZ81.

Synthesis and biological activity of heteroprostanooids: 92UK456.

Synthesis of natural bioactive heterocyclic compounds: 92YZ516.

The use of asparaginic acid in the synthesis of drugs: 91YGK26.

b. *Definite Types of Activity.* Alkaloids of *Vinca*, mantansinoids, and macrocyclic lactones of the risoxine type as antimyothotics: 91YGK892.

Antagonists of serotonin receptor: 91SL213.

Antimetabolites of nucleic acids as antitumor agents: 91YGK989.

Artemisinin (3,6,9-trimethyl-9,10*b*-epidioxyperhydropyrano[4,3,2-*jk*] benzoxepin-2-one), a new type of antimalarial drug: 92CSR85.

Carboranes and organoboron derivatives of heterocycles in electron-capture therapy for cancer: 93AG(E)950.

Chemically modified anthracycline antibiotics as chemotherapeutic agents: 91YGK1002.

Chemistry and biology of immunosuppressant (–)-FK-506 (containing piperidine and tetrahydropyran fragments): 92YGK522.

Chiral N- and N,O-heterocycles as agonists and antagonists of  $\alpha$ - and  $\beta$ -adrenoceptors: 91T9953.

Derivatives of 5- and 6-membered heterocycles as cardiotonics: 92KFZ(3)4.

Features of antibacterial action of derivatives of 4-quinolone-3-carboxylic acid: 93KFZ(5)4.

Heterocycles as  $\beta$ -adrenoblockers: 91KFZ(5)21.

Heterocycles as antitumor agents: 91YGK968, 91YGK980; 92FES1115.

Heterocycles as ligands in metalloenzymes acting as Lewis acids: 92ACR273.

Heterocycles as selective muscarine ligands recognizing choline receptors: 92KFZ(1)4.

Heterocycles with depressant activity: 93KFZ(7)4.

N-Heterocycles as inhibitors of xanthine oxidase: 91RTC139.

N-Heterocycles in therapy of micoses: 93KFZ(4)12.

Neuropharmacologic activity of piperidine derivatives: 91KFZ(7)20.

New analogs of purine nucleosides possessing antitumor and antiviral properties: 93JMC635.

Photoimmunotoxins (sensitizers for photodynamic therapy of tumors): 93KFZ(10)7).

Synthesis and antitumor activity of camphotecine analogs: 91YGK1013.

Synthesis of analogs of *cis*-platinum-bearing heterocyclic substituents and Pt(II) chelates: 91YGK1021.

Synthesis of pyrimidine derivatives with cytostatic activity: 92WCH377.

c. *Individual Substances and Groups of Compounds.* Biological activity of furan derivatives: 93KGS291.

Drugs, derivatives of  $\gamma$ -substituted piperidines: 91KFZ(7)61.

Enzymatic synthesis of aza sugars as inhibitors of carbohydrate metabolism: 93ACR182.

Fused pyrimidines inhibiting enzymes active in metabolism of folic acid as new antitumor substances: 91KFZ(9)20.

1-(2-Hydroxyethoxy)methyl-6-phenylthiothymine as an agent active against HIV-1: 91YGK1142.

Lipase-catalyzed synthesis of chiral 1,4-dihydropyridines and barbiturates as drugs: 91YGK1127.

Medicinal chemistry of cyclic peptides: 91AG(E)1278.

Pharmacokinetics of fluoroquinolones: 93MI23.

Phosphorus derivatives of heterocycles possessing antiinflammatory and analgesic activity: 92KFZ(7/8)21.

N-Substituted amides, derivatives of saturated N-heterocycles, antiarithmetic and local-anesthetic activities of: 91UK852.

Synthesis of chiral and bioactive fluorinated heterocycles: 93T9385.

Synthesis of heterocycles of unknown types as potential drugs: 91SL667.

Synthesis of ftorafur: 91KGS1590.

Uses of new fluoroquinolones: 93MI26.



X-ray diffraction study of monocrystals of oligonucleotides and oligonucleotide-drug complexes: 91AG(E)1254.

## 6. *Pesticides*

Herbicides as inhibitors of photosynthesis: 91AG(E)1621.

Heterocycles as pesticides: 91AG(E)1193.

Heterocycles with pesticide activity as ligand-active agents: 89MI1.

Metabolism of pesticides possessing heterocyclic fragments: 92UK1932.

Pyrethroids containing heterocyclic fragments: 92MI4.

## 7. *Miscellaneous*

a. *General.* Chemical mechanisms of resistance of bacteria to  $\beta$ -lactam antibiotics: 92MI36.

O-, S-, and O,S-Heterocyclic compounds, intermediates and by-products of chemical industry, use in the synthesis of biologically active substances: 91MI59.

Nucleosides and their derivatives with antiviral properties: 92MI33.

b. *Enzymes, Coenzymes, and Their Models.* Heterocycles as glycosidase inhibitors: 91YGK846.

N-Heterocycles as ligands in oxygenase analogs: 93IZV272.

Heterocyclic compounds including macroheterocycles and polymers with heterocyclic fragments as enzyme mimics: 90MI1.

Quinoproteins, enzymes containing quinoid cofactors, e.g., pyrroloquinolinequinone and triptophanequinone: 91MI35.

c. *Amino Acids and Peptides.* Artificial amino acids containing heterocyclic fragments: synthesis and biological importance: 87MI2.

Carnosin and anserin, dipeptides containing histidine or methylhistidine units: 92MI34.

Cyclopeptides and peptides with N-heterocyclic fragments as peptidomimetics: 93AG(E)1244.

Detoxin complex group of depsipeptide metabolites from *Streptomyces caespitosus* subsp. *detoxicus* 7072 GC and other *Streptomyces* species: 93H(36)359.

Glycylleicylprolin and its analogs: 92MI32.

Modified 7- and 10-membered cyclic peptides as mimetics of peptide secondary structure: 93SL821.

NMR of cyclic peptides: 92CSR227.

Quantitative analysis and prediction of hydrophoby of cyclic oligopeptides: 91YGK836.

Structure and activity of cyclic neuropeptides of insect brain: 92YGK545.

Use of  $\beta$ -alanine-L-histidine (carnosine) in medicine: 92MI35.

d. *Plant Metabolites*. Bryophytes as a source of bioactive compounds: 91AG(E)130.

Chemistry and bioactivity of artemisinin and related antimalarials: 91H(32)1593.

6,9-Epoxy cyclodeca[*b*]furan sesquiterpenoids: 92H(34)807.

Heterocycles from higher plants having antitumor and cytotoxic properties: 93H(35)1467.

S-Heterocycles of genus *Allium*: 91PS(58)3; 92AG(E)1135.

Isolation of bioactive heterocycles from plants: 92YGK963.

Phytochrome: visual pigment of plants: 91AG(E)1216.

Sesquiterpene lactones: 90MI11.

Synthesis of diterpenoids containing O-heterocyclic fragments: 91MI41.

Synthesis of fungal metabolites, cytochalasins: 91ACR229.

Synthesis of taxol (an antitumor semisynthetic terpenoid containing an oxetane fragment): 93MI33.

e. *Heterocycles Produced by Marine Organisms*. Bioactive compounds of marine origin relative to phenols containing heterocyclic fragments: 91MI58.

Bioactive cyclic peptides and peptides containing O-heterocyclic fragments from sponges: 93CRV1793.

Bioactive cyclic polyethers from marine organisms: 91MI57.

Bioactive heterocycles from sea microorganisms: 92YGK772.

Biosynthesis of marine O-, N-, and N,O-heterocycles: 93CRV1699.

Heterocycles from sea bacteria: 93CRV1673.

Heterocycles in marine organisms: 89MI4; 91MI26.

N- and O-Heterocycles bioactive metabolites of symbiotic marine microorganisms: 93CRV1753.

N- and O-Heterocycles, metabolites of sea microalgae: 93CRV1685.

Heterocyclic amino acid-based metabolites produced by ascidians: 93CRV1771.

Marine products containing indole fragments, structures and syntheses: 91H(32)1391.

Marine products containing quinoline and/or isoquinoline fragments, structures and syntheses: 91H(32)759.

Marine toxins (fused saturated N- and O-heterocycles): 93CRV1897.

Metalloporphyrins in marine organisms: 92WCH343.

Natural antitumor agents of marine origin: 91Y GK1053.

Porphyrins, alkaloids, antibiotics and other marine metabolites as chelating agents: 93AG(E)1.

Structure, synthesis, and biochemistry of marine pyridoacridine alkaloids: 93CRV1825.

Synthesis of marine nonterpene natural products containing heterocyclic fragments: 92MI14.

Synthesis of marine terpenoids containing heterocyclic fragments: 92MI13.

Total synthesis of marine cytotoxic cyclic peptides: 91YZ1.

f. *Other Topics.* Chemical synthesis of DNA and DNA analogs: 91ACR278.

Enzymatic synthesis of bioactive natural heterocycles and their analogs: 92PAC1933.

Formation and antitumor activity of homoazasteroid derivatives: 93JHC1.

Heterocycles as reversible MAO inhibitors: 91KFZ(8)4.

N- and O-Heterocycles in chemical defense of invertebrates: 93CRV1911.

Mechanism of imidazole catalysis of RNA cleavage by enzymes and enzyme models: 91ACR317.

Molybdenum cofactor, its biological importance and structural and synthetic aspects: 93H(35)1551.

Oxidosqualene in the biosynthesis of triterpenes and steroids: 93CRV2189.

Polychlorinated dibenzodioxines and dibenzofurans as xenobiotics: 91UK536.

Psychopharmacologic properties of endogenic pyrimidine nucleosides: 91KFZ(6)4.

Secondary metabolites of *Streptomyces* sp. inhibiting oncogenic functions: 91Y GK1062.

Semisynthetic modifications of insulin: 91CLY1105.

Synthesis of azacyclic prostaglandin analogs: 93KFZ(2)48.

Synthesis of podophyllotoxin and related fused compounds containing hydrofuranone and 1,3-dioxole fragments: 92S719.

Teleocidines (indole 9-membered azalactams produced from amino acids) as models for establishing the mechanism of tumor growth: 91Y GK1070.

Transition metal complexes with heterocyclic ligands as models of flavaenzyme and cytochrome P<sub>450</sub>: 92PAC403.

X-ray diffraction study of monocrystals of oligonucleotides and oligonucleotide-drug complexes: 91AG(E)1254.

### III. Three-Membered Rings

#### A. GENERAL TOPICS

Oxiranes and aziridines in photoinitiated [3 + 2]-cycloaddition reactions: 93CRV93.

#### B. ONE HETEROATOM

##### 1. *One Nitrogen Atom*

3-Amino-2*H*-azirines as amino acid equivalents: 86IJ3.

3-Amino-2*H*-azirines as synthons for  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids in the synthesis of heterocycles and peptides: 91AG(E)238.

Asymmetric synthesis of aziridines with participation of 1-haloalkyl aryl sulfoxides: 92SL455.

Carbene synthesis of aziridines: 90MI4.

Ring opening of aziridines and azirines by hydrofluorination: 91T5329.

Synthesis of *N*-arylaziridines based on 1-chloroalkyl(aryl)sulfoxides: 91YZ205.

##### 2. *One Oxygen Atom*

a. *Reactivity of Oxiranes.* Addition reaction of epoxides with esters and its use in synthesis of polymers: 91YGK218.

*O*-Benzylglycidol as a chiral building block in the synthesis of bioactive natural products: 91YZ647.

Chiral Lewis acids as catalysts in asymmetric ring opening of epoxides: 91S1.

Differences in behavior of oxiranes and oxetanes by cationic cyclo-oligomerization and polymerization: 93T8707.

Enantioselective rearrangement of epoxides to allylic alcohols: 91TA1.

Photochemical reactions of glycidyl esters: 92MI11.

Rearrangements of epoxyalcohols and related compounds: 90OPP547.

Regio- and stereoselective intramolecular cyclizations of epoxides: 92Y GK638.

Ring opening of oxiranes by hydrofluorination: 91T5329.

b. *Synthesis of Oxiranes.* Asymmetric epoxidation: 91UK241.

Asymmetric synthesis of oxiranes with participation of 1-haloalkyl aryl sulfoxides: 92SL455.

Enantioselective preparation of nonfunctionalized oxiranes: 92CRV873.

Epoxidation induced by transition metal complexes with N-heterocycles as ligands: 92YGK997.

Mechanism of alkene epoxidation by oxometalloporphyrins containing hypervalent Fe, Cr, and Mn atoms: 92ACR314.

Sulfonium ylides in synthesis of optically active epoxides: 93PS(74)215.

Syntheses and reactions of chiral acetylenic oxiranes: 92BSB415.

Syntheses of nonracemic glycidol and related 2,3-epoxy alcohols: 91CRV437.

Synthesis of oxiranes based on 1-chloroalkyl(aryl)sulfoxides: 91YZ205.

### 3. *One Sulfur Atom*

Advances in thiirane chemistry: 93MI16.

Anionic copolymerization of thiiranes with elemental sulfur: 91PS(59)47.

Polymerization of thiiranes: 93PS(74)71.

Synthesis and reactions of alkylidenepisulfides: 91PS(58)179.

## C. TWO HETEROATOMS

### 1. *Two Nitrogen Atoms*

$S_N2$  and electron-transfer initiated reactions of halodiazirines: 92ACR31.

### 2. *One Nitrogen and One Oxygen Atom*

Electrophilic amination with oxaziridines: 91S327.

N-Sulfonyloxaziridines as reagents in asymmetric hydroxylation of enolates: 92CRV919.

### 3. *One Oxygen and One Sulfur Atom*

Oxathiiranium S-ylides: 91PS(58)275.

## D. THREE HETEROATOMS

Dioxathiiranium and oxathiaziridinium S-ylides: 91PS(58)275.

## IV. Four-Membered Rings

### A. GENERAL TOPICS

Electrocyclic reactions in the chemistry of 4-membered heterocycles: 93KGS1155.

### B. ONE HETEROATOM

#### 1. *One Nitrogen Atom*

Alkylation of ambident nucleophilic hydroxamates by 4-substituted 2-azetidinones: 93H(35)1205.

Asymmetric synthesis of azetidinones: 91PHC1.

2,3-Dihydroazete 1-oxides, synthesis and reactivity: 90BSF704.

Four-component condensation in the synthesis of  $\beta$ -lactams: 91MI19.

$\beta$ -Lactam ring formation: 92YGK112.

Oxacephems, artificial  $\beta$ -lactam antibiotics: 91YZ77.

Synthesis of 3-amino-2-azetidinones: 91T7503.

Synthesis of homochiral  $\beta$ -lactams from N-protected  $\alpha$ -aminoimines using an asymmetric [2 + 2]-cycloaddition reaction: 92BSB541.

Synthesis of  $\beta$ -lactams from carbohydrate precursors: 92WCH821.

#### 2. *One Oxygen Atom*

Advances in  $\beta$ -lactone chemistry: 93S441.

Differences in behavior of oxiranes and oxetanes by cationic cyclo-oligomerization and polymerization: 93T8707.

### C. TWO HETEROATOMS

#### 1. *Two Nitrogen Atoms*

2,4-Diimino-1,3-diazetidines, preparation from iminophosphoranes and reactivity: 93JPR305.

#### 2. *One Nitrogen and One Oxygen Atom*

Oxo and imido functionalized 1,2-oxazetidines: 93JHC579.

### 3. *Two Oxygen Atoms*

Formation of 1,2-dioxetanes by photooxidation of 1,3-dienes: 91T1343.

## V. Five-Membered Rings

### A. GENERAL TOPICS

Activated cyclopropanes in the synthesis of 5-membered heterocycles: 93UK887.

*N*-Aminoazoles: 92AHC(53)85.

1,3-Dipolar cycloaddition reactions of azolopyridazines with diazoalkanes: 91T2925.

Electrochemistry of azoles: 90MI12.

Halogenation of 5-membered heterocycles: 93AHC(57)291.

Reactions of 5-membered heterocycles with 1,2-bis-(arylsulfonyl)alkenes as dienophiles: 91OPP571.

Ring transformations in 5-membered heterocycles: 93AHC(56)49.

Synthesis of fused azapentalenes using the Weiss reaction: 91T3665.

Trimethylsilyldiazomethane in the synthesis of azoles: 91YZ570.

### B. ONE HETEROATOM

#### 1. *General*

Reactivity of 5-membered heteroaromatics toward electrophiles in the gas phase: 91PAC243.

#### 2. *One Nitrogen Atom*

a. *Monocyclic Pyrroles.* 1-Hydroxypyrroles and 9-hydroxycarbazoles: 90AHC(51)105.

Preparation of pyrrole metal complexes and their use in organic synthesis: 92MI29.

Preparation of pyrroles from ketoximes and acetylenes: 90AHC(51)177.

Pyrrole derivatives with phosphorus-containing substituents: 93MI1.

Pyrroles, general monograph: 90CH(48,1)1; 92CH(48,2)1.

Synthesis, structure, and properties of vicinal hydroxy-, mercapto-, and hydroselenoaldimines of the pyrrole series: 92MI22.

b. *Hydropyrroles*. Chemistry of tetramic acid (4-hydroxy-3-pyrrolin-2-one derivative): 93AHC(57)139.

Chiral amides, pyrrolidine derivatives, in asymmetric synthesis: 92PAC1849.

Chiral nonracemic bicyclic  $\gamma$ -lactams in the synthesis of compounds with quaternary carbon centers: 91T9503.

Generation of N-centered radicals and their cyclization to give pyrrolidines: 93AHC(58)1.

Pyrrolidine and pyrrolidone derivatives with phosphorus-containing substituents: 93MI1.

c. *Pyrrole Pigments*. Biosynthesis of linear tetrapyrrole chromophores of chromoproteins: 93CRV785.

d. *Porphyrins and Related Systems*. Biosynthesis of vitamin B<sub>12</sub>: 93ACR15.

Chemistry and biochemistry of N-substituted porphyrins: 87MI1.

Chiral semicorrins and related N-heterocycles as ligands in asymmetric catalysis: 93ACR339.

Chlorophyll as electron donor: 92CLY113.

Chlorophyll derivatives in photochemical decomposition of nucleic acids: 91YGK762.

Complexes based on porphyrins as artificial enzymes: 93CRV2295.

Complexes of porphyrins with highly charged cations of p-, d-, and f-metals: 93KK171.

Electrochemistry of porphyrins: 91MI14.

Electrochemistry of pyropolymers obtained on pyrolysis of charge-transfer complexes of transition metals with porphyrins and phthalocyanins: 90MI17.

Electronic and steric effects in the coordination sphere of porphyrin and phthalocyanine complexes: 93KK358.

Fine structure of X-ray absorption spectra of heme-containing oxygenases and peroxidases: 91MI16.

Gene-engineering synthesis of porphyrins and corrins: 92T2559.

Mechanism of alkene epoxidation by oxometalloporphyrins containing hypervalent Fe, Cr, and Mn atoms: 92ACR314.

Mechanism of oxidation with potassium monopersulfate-metalloporphyrin systems: 92NJC203.

Mechanism of photosynthesis with participation of porphyrins: 93ACR198.

Metallotetraarylporphyrins as models of cytochrome P<sub>450</sub>: 93G579.



Metallotetraphenylporphyrins, reactions with hydroperoxides in aqueous solutions: 91ACR243.

Metal-metal multiple bonds in 4*d*- and 5*d*-metalloporphyrin dimers: 93ACR586.

Phthalocyanine and related metal complexes with specific electrical and optical properties: 91MI17.

Porphyrins and phthalocyanines in artificial photosynthesis: 92CRV435.

Porphyrins as indicators in studies of solvate complexes of transition metals: 91UK1946.

Porphyrins as photosynthetic model systems: 91MI46.

Porphyrins bearing quaternary pyridinium substituents: 93KGS723.

Porphyrins in photoinduced electron tunneling: 92MI15.

Sapphirins ("extended porphyrins", cyclic pentapyrroles): 91SL127.

Synthetic approach to the porphyrin chemistry: 91AJC1163.

Synthesis of porphyrin-based molecular complexes as models for the study of photosynthesis: 93UK1020.

Template synthesis of porphyrins: 93ACR469.

e. *Indoles and Hydroindoles*. Chemistry of 1-hydroxyindoles and their derivatives: 91YGK205.

Fulgides of the indole series: 92KGS744.

NMR spectra of polyalkylindoles: 93KGS899.

Structure, properties, and functions of melanines (containing 5,6-indoloquinone and benzothiazole fragments): 91WCH169.

Synthesis of biindole alkaloids possessing antitumor activity: 91SL11.

Synthesis of 5- and 6-hydroxyindoles using the Nenitzescu reaction: 93KFZ(6)37.

Tryptophan in peptide synthesis: 90OPP655.

f. *Isoindoles (Including Phthalocyanines)*. Synthesis of isoindolinium and dihydroisoindolinium salts and their fused analogs: 93KGS435.

g. *Polycyclic Systems Including Two Heterocycles*. Approaches to the synthesis of antitumor pyridocarbazole alkaloids: 91SL289.

Pyrrolo[1,2-*a*]pyrazines, synthesis and properties: 91KGS1299.

Pyrroloquinolines: 91OPP67.

Substituted 10*H*-pyrido[1,2-*a*]indolium salts, synthesis: 91MI24.

Synthesis and properties of 1,2-dihydropyrrolizines: 92KGS147.

### 3. *One Oxygen Atom*

a. *Furans*. Biological activity of furan derivatives: 93KGS291.

Catalytic reactions of furans: 93KGS1174.

Catalytic synthesis and transformations of furans: 92MI21.

Furan analogs of tetracyanoquinodimethane as new organic metals: 92MI23.

Furan compounds as precursors of chiral synthons in enzymatic synthesis of carbohydrates: 91S509.

Furan in the synthesis of cyclacenes: 92CSR215.

Furyl-substituted silatranes and germatranes: 92KGS725.

Mass spectra of furan derivatives of Si, Ge, and Sn: 93KGS891.

NMR spectra of furan derivatives of IVB group elements: 93KGS879.

Preparation of furans in Pd-catalyzed reactions of propargyl carbonates: 92YGK908.

Reactions of furans: 92MI5.

Reactions of substituted furan derivatives with Grignard reagents: 92MI19.

Synthesis and properties of unsaturated nitro compounds of the furan series: 93UK184.

Synthesis and reactions of nitroalkyl derivatives of the furan series: 92MI20.

Synthesis, structure, and properties of vicinal hydroxy-, mercapto-, and hydroselenoaldimines of the furan series: 92MI22.

b. *Hydrofurans*. Preparation of 2,3-dihydrofurans in Pd-catalyzed reactions of propargyl carbonates: 92YGK908.

Samarium(II) iodide in the synthesis of tetrahydrofuran and dihydrobenzofuran derivatives: 92SL943.

Synthesis of CF<sub>3</sub>-substituted tetrahydrofurans: 91YGK624.

c. *Benzannulated Furans*. Polychlorinated dibenzofurans: 91CLY158.

Synthesis and reactions of fused furan derivatives: 92MI6.

Synthesis of 5-hydroxybenzofurans using the Nenitzescu reaction: 93KFZ(6)37.

d. *Terpenoids Including a Five-Membered Ring with One Oxygen Atom*. Triterpenoids with  $\alpha$ -furyl substituents: 89MI3.

e. *Miscellaneous Bi- and Polycyclic Systems*. Photochemical reactions of furocoumarin and related compounds: 91YGK809.

Synthesis and reactions of fused furan derivatives: 92MI6.

f. *Five-Membered Lactones*. Asymmetric synthesis based on  $\gamma$ -alkoxybutenolides: 92BSB627.

Asymmetric synthesis using  $\gamma$ -alkoxybutenolides: 92PAC1865.

Synthesis and reactions of 2,3,4-furantriones (2,3-dioxobutyrolactones): 92AHC(53)233.

Synthesis of optically pure  $\gamma$ -lactones using asymmetric reduction by baker's yeast: 91YGK647.

Synthesis of polycyclic podophilotoxin  $\gamma$ -lactones: 91SL11.

Synthesis of  $\gamma$ -lactones from unsaturated alcohols and CO catalyzed by Pd complexes: 91YGK909.

Synthesis of terpenoid compounds from tricyclic  $\gamma$ -lactone  $\alpha$ -santonin: 93T4761.

#### 4. *One Sulfur Atom*

a. *Thiophenes*. Annulation effects in the thiophene series: 91PHC21.

Biologically active thiophene derivatives: 91CH(44,4)397.

Bithienyls and polythienyls: 92CH(44,5)755.

Chemistry of thiophenium ions: 92KGS733.

Conducting charge-transfer salts based on thiophene analogs of tetracyanoquinodimethane: 91CSR355.

Desulfurization of thiophene on metal surfaces and with organometallic complexes: 92CRV493.

Electrochemistry of poly(thiophene): 90MI17.

Electrophilic trichloromethylation of thiophenes: 93KGS980.

Formation of thiophene derivatives on chalcogenation in multiphase superbase systems: 92MI24.

Halothiophenes, reactions with thiyl radicals: 91PS(58)151.

Mass spectra of thiophene derivatives of Si, Ge, and Sn: 93KGS891.

Mechanism of hydrogenolysis of thiophene on bimetallic sulfide catalysts: 92UK332.

Naturally occurring alkynylthiophenes and polythiophenes: 88MI2.

New synthesis of thiophenes using reductive condensation of  $\beta,\beta'$ -diketosulfides: 93PS(74)157.

Nitrile oxides of the thiophene series, synthesis and reactivity: 91MI45.

Nucleophilic substitution in the thiophene series: 91CH(44,4)295.

Organometallic derivatives of thiophenes: 92CH(44,5)257.

Physical properties of thiophene derivatives: 91CH(44,4)1.

Synthesis, functionalization, and uses of conjugated poly(thiophenes): 92CRV711.

Synthesis of thiophenes with the participation of thiyl radicals: 91PS(58)151.

Synthetic applications of ring opening and cycloaddition of thiophene-1,1-dioxides: 93PS(74)113.

Synthesis, structure and properties of vicinal hydroxy-, mercapto-, and hydroselenoaldimines of the thiophene series: 92MI22.

Thienyl-substituted silatranes and germatranes: 92KGS725.

Thiophene analogs of tetracyanoquinodimethane as new organic metals: 92MI23.

Thiophenethiols: 91UK2528.

Vinylthiophenes and thienylacetylenes: 92CH(44,5)1.

b. *Annulated Thiophenes*. Asymmetric synthesis of 5,6-dihydro-7*H*-thieno[2,3-*b*]thiopyran 4,4-dioxide derivatives as carboanhydrase inhibitors: 92JHC627.

Conducting charge-transfer salts based on thienothiophene analogs of tetracyanoquinodimethane: 91CSR355.

Synthesis of thienothiophenes with the participation of thiyl radicals: 91PS(58)151.

Synthesis, structure, and properties of vicinal hydroxy-, mercapto-, and hydroselenoaldimines of the benzo[*b*]thiophene series: 92MI22.

Tricyclic fused thiophenes, a chapter in a general monograph: 92CH(44,5)755.

c. *Hydrothiophenes*. Methods for the synthesis of nitro-substituted thiolene-1,1-dioxides: 93ZOB241.

## C. TWO HETEROATOMS

### 1. *General*

Direct polycondensation of benzazoles: 92SL605.

### 2. *Two Nitrogen Atoms*

a. *Pyrazoles*. Advances in the chemistry of poly(pyrazoly)borates (scorpionates): 93CRV943.

Poly(pyrazoly)borate complexes of Sn(II) and Pb(II): 92SL469.

Synthesis, structure, and properties of vicinal hydroxy-, mercapto-, and hydroselenoaldimines of the pyrazole series: 92MI22.

b. *Hydropyrazoles*. Fluoro- and difluoromethylene-substituted  $\Delta^1$ -pyrazolines, formation in cycloaddition reactions with participation of fluoroallene and 1,1-difluoroallene: 91ACR63.

Pyrazolidinones, general review: 91OPP273.

c. *Annulated Pyrazoles.* Synthesis and properties of functionally substituted pyrazolidines: 92KGS829.

Synthesis of pyranopyrazoles: 91G185.

Synthesis of 1*H*-pyrazolo[1,5-*b*]-1,2,4-triazole and its use in preparation of bright red dyes for color photography: 91YGK541.

d. *Imidazoles.* Histidine in peptide synthesis: 90OPP655.

Imidazole *N*-oxides: 93KGS147.

Mechanism of hydrolysis of *N*-acylimidazoles: 93ACR325.

Synthesis and properties of bridged biimidazoles: 91T6851.

e. *Annulated Imidazoles.* Mechanism of hydrolysis of *N*-acylbenzimidazoles: 93ACR325.

Synthesis and properties of imidazo[1,2-*c*]pyrimidines: 91WCH177.

Synthesis and thermal and photochemical reactions of benzimidazole 1,3-dioxides: 93H(35)1503.

### 3. *One Nitrogen and One Oxygen Atom*

a. *1,2-Heterocycles.* [3 + 2]-Cycloaddition of nitronic esters and nitro compounds: 93CRV725.

2,1-Benzisoxazoles (anthranils), synthesis and transformation to other heterocycles: 91KFZ(1)57.

Fluoro- and difluoromethylene-substituted isoxazolidines, formation in cycloaddition reactions with the participation of fluoroallene and 1,1-difluoroallene: 91ACR63.

Isoxazolidines: 91CH(49,1)649.

Isoxazolines: 91CH(49,1)417.

Isoxazoles, general monograph: 91CH(49,1)1.

New synthesis of *N*-heterocycles on rearrangement of spiro-5-isoxazolines: 93SL1.

Nitrile oxides in the synthesis of isoxazoline and isoxazole derivatives: 91MI45.

Regio- and stereoselective syntheses of isoxazolidines bearing phosphinyl substituents: 91G285.

Regio- and stereoselectivity in the chemistry of 2-isoxazolines: 92YGK808.

Synthesis and properties of functionally substituted isoxazolidines: 92KGS829.

b. *1,3-Heterocycles.* Advances in oxazole chemistry: 93H(35)1441.

Chiral 2-oxazolones in the synthesis of 2-aminoalcohols: 91YGK118.

Mesoionic oxazoles: 86CH(45)731.

Oxazoles, general monograph: 86CH(45)1.

Oxazoles, spectral properties: 86CH(45)343.

Oxazoles and oxazolines in organic synthesis: 86CH(45)963.

Oxazolidin-3-yl as a protecting group in asymmetric synthesis: 92 PAC1889.

Oxazolones: 86CH(45)361.

(5*H*)Oxazolones and their salts, synthesis and transformations: 91 KGS723.

Oxazolones in the synthesis of fluorine-containing aromatic amino acids: 91UK2047.

Oxazolo[3,2-*a*]pyridinium system, synthesis: 91KGS1155.

Reactions of 5-oxo-4,5-dihydrooxazoles with O-nucleophiles: 93UK55.

Syntheses of oxazolones from L-tryptophan and  $\alpha$ -haloacetic anhydrides, and their reactions: 92BSB643.

Synthesis of natural oxazoles: 92JHC607.

#### 4. *One Nitrogen and One Sulfur Atom*

a. *General.* Oxidation of 5-membered N,S-heterocycles: 90PHC1.

Trithiazyl trichloride in the synthesis of 5-membered N,S-heterocycles: 92JHC639.

b. *1,2-Heterocycles.* Asymmetric thermal reactions with Oppolzer camphorsultam: 93T293.

Saccharin in the Gabriel synthesis of primary amines: 91ACR285.

c. *1,3-Heterocycles.* Addition reactions of 1,3-thiazole-5(4*H*)-thiones in syntheses of spirocyclic and fused bicyclic S-heterocycles: 91PS(58)281.

Azorodanines and their analytical use: 92ZAK1157.

Diastereoselective synthesis of carbohydrates and related compounds using functionalized thiazoles: 92BSB433.

Divinyldisulfides, thiamin derivatives: 92MI17.

Structure, properties, and functions of melanines (containing 5,6-indoloquinone and benzothiazole fragments): 91WCH169.

Synthesis of bioactive triazolobenzothiazoles: 92YGK875.

Synthesis of natural thiazoles: 92JHC607.

Synthesis of thiazole amino acids as precursors of marine cytotoxic cyclic peptides: 91YZ1.

Synthesis of thiazolo[3,2-*a*]pyrimidines: 91MI49.

Thiazolo[3,2-*a*]pyridinium system, synthesis: 91KGS1155.

### 5. *Two Oxygen Atoms*

Modified chiral biphosphinic dioxolane ligands and their use in the asymmetric synthesis of natural lignans: 92H(33)435.

### 6. *One Oxygen and One Sulfur Atom*

Formation of 1,3-oxathiolane derivatives on chalcogenation in multi-phase superbase systems: 92MI24.

### 7. *Two Sulfur Atoms*

a. *1,2-Heterocycles.* Dithiolene dyes and their transition-metal complexes: 91T909.

1,2-Dithiolo-1,2-dithioles, thermolysis and photolysis of: 91PS(58)179.

Structure of trithispentalenes and related compounds 91PS(58)17.

Synthesis and properties of new functionalized tetrathiafulvalene  $\pi$ -electron donors: 93PS(74)279.

Synthesis, reactions, and properties of 1,2-tetrachalcogenafulvalenes: 93MI15.

b. *1,3-Heterocycles.* Conducting charge-transfer salts based on bis-ethyldithiotetrathiafulvalene: 91CSR355.

1,3-Dithiolanes and 1,3-dithiolenes, formation in pericyclic reactions of alkenes and acetylenes with anions of dithiocarboxylic acids: 91PS(58)255.

Fused systems based on tetrathiafulvalene as new organic metals: 92MI23.

Synthesis and reactions of benzo-1,3-dithioles, -diselenoles, and -telluroles: 93MI18.

Synthesis, reactions, and properties of 1,3-tetrachalcogenafulvalenes: 93MI15.

## D. THREE HETEROATOMS

### 1. *Three Nitrogen Atoms*

a. *Monocyclic Systems.* Molecular rearrangements of 1,2,3-triazolines: 91MI9.

Synthesis and ring-chain tautomers of 1,2,4-triazolidine-3-thiones: 93KGS991.

b. *Annulated Triazoles*. Benzotriazole, use in organic synthesis: 91T2683.  
 $\alpha$ -Hydrazino-substituted heterocycles and their hydrazones in the synthesis of annulated 1,2,4-triazoles: 93KGS1587.

Synthesis of bioactive triazolobenzothiazoles: 92YGK875.

Synthesis of 1*H*-pyrazolo[1,5-*b*]-1,2,4-triazole and its use in preparation of bright red dyes for color photography: 91YGK541.

## 2. *Two Nitrogen Atoms and One Oxygen Atom*

Rearrangements of benzofuroxanes and their analogs: 93H(35)483.

Synthesis of 3,5-diaryl-1,2,4- and 2,5-diaryl-1,3,4-oxadiazoles from trichloromethylarenes: 93KGS980.

## 3. *Two Nitrogen Atoms and One Sulfur Atom*

Synthesis and ring-chain tautomerism of 2-amino-1,3,4-thiadiazolines: 93KGS991.

## 4. *One Nitrogen Atom and Two Sulfur Atoms*

1,2,3-Dithiazoles: 92JHC639.

## 5. *Three Oxygen Atoms*

Structure and mechanism of formation of ozonides (1,2,3- and 1,2,4-trioxolanes): 92CSR79.

## 6. *Two Oxygen Atoms and One Sulfur Atom*

Synthesis of chiral sulfoxides through 5-membered cyclic sulfites of ethyl lactate: 91PS(56)89.

## 7. *Three Sulfur Atoms*

Structure of trithiapentalenes and related compounds: 91PS(56)245.

# E. FOUR HETEROATOMS

## 1. *Four Nitrogen Atoms*

Phase-transfer catalysis in tetrazole chemistry: 92KGS754.

Reaction of 5-aryltetrazoles with *N*-arylbenzimidoyl chlorides to give substituted 1,2,4-triazoles and 3*H*-1,3,4-benzotriazepines: 93KGS907.



Tetrazolium salts, preparation on oxidation of formazanes and properties: 92MI12.

## VI. Six-Membered Rings

### A. GENERAL

Anomeric effect in 6-membered O- and S-heterocycles: 92T5019.

1,3-Dipolar cycloaddition reactions of pyridines and azolo- and azino-pyridazines with diazoalkanes: 91T2925.

Directed metallation of pyridines, quinolines, and diazines: 91AHC (52)187.

*N*-Fluoroquinuclidinium salts as fluorinating agents: 92YGK338.

Kost-Sagitullin rearrangement in the pyridine, pyrazine, and pyrimidine series 92MI27.

Molecular design and synthesis of 6-membered heteroaromatics: 93 KGS937.

New recyclizations and transformations of azines: 92KGS792.

Nitroazines, a monograph covering derivatives of pyridine, diazines, and triazines: 91MI7.

### B. ONE HETEROATOM

#### 1. *One Nitrogen Atom*

a. *Pyridines.* Advances in the chemistry of 3-cyanopyridin-2(*H*)-ones, -thiones, and -selenones: 92MI45.

Diels-Alder cycloaddition of 2-pyridones: 92T9171.

Ligand exchange in sulfuranes containing 2-pyridinyl substituents: 91 PS(59)79.

3-Nitropyridines, synthesis of: 91KGS867.

Pyridylphosphines: 93CRV2067.

Reactions of pyridines and their *N*-oxides with carboxylic acids: 92 WCH103.

Regioselective synthesis of substituted 3-cyano-2(1*H*)-pyridinethiones and -selenones from unsymmetrical *p*-enaminoketones: 90MI5.

Selective catalytic hydrogenation of the pyridine ring in arylpyridines and fused pyridine systems: 92KGS1443.

Single-electron transfer and nucleophilic substitution in the pyridine series: 92NJC131.

Template effect of Cu(I) in synthesis of catenanes and molecular knots possessing pyridine fragments: 92BSF113.

b. *Pyridinium Compounds, Ylides, Pyridine N-Oxides.* *N*-Fluoropyridinium salts as fluorinating agents: 92YGK338.

*N*-(Oxidophenyl)pyridinium betaine dyes: 92CSR147.

Porphyrins bearing quaternary pyridinium substituents: 93KGS723.

Synthesis of *N*-(4-pyridyl)pyridinium salts from trichloromethylarenes and pyridine: 93KGS980.

c. *Applications of Pyridines.* Homogeneous and heterogeneous synthesis of redox polymers and copolymers  $[M(4\text{-vinyl-4-methyl-2,2'-bipyridine})_3](PF_6)_2$  ( $M = Ru, Os$ ): 93SL375.

Oligopyridines as helicine-type ligands: 92T10013.

Preparation and use in asymmetric synthesis of chiral ligands based on pyridine skeleton: 92G89.

Silylated azomethineylides and thiocarbonylides in the synthesis of heterocycles: 92YGK48.

Pyridine derivatives as photosynthetic model systems: 91MI47.

d. *Bipyridines and Related Systems.* Bipyridinium salts as electron relays for photoreduction of water: 91JHC827.

Bridged bipyridines and terpyridines, fused systems with several pyridine rings or with indole and pyridine fragments simultaneously, rigid pyridinophanes: 91T6851.

1,3-Dipolar cycloaddition reactions of pyridines with diazoalkanes: 91T2925.

Electrochromic properties of polymeric viologens: 90MI17.

Viologens (4,4-bipyridinium salts), chemistry: 91H(32)2241.

e. *Hydropyridines.* Chemistry of hydrogenated 3-cyanopyridine-2(1*H*)-thiones and -selenones: 93PS(74)139.

Chemistry of 3-piperideines: 93KGS913.

Chiral nonracemic bicyclic  $\delta$ -lactams in the synthesis of compounds with quaternary carbon centers: 91T9503.

Reactions of 1,4-dihydropyridines: 93KGS579.

Some substitution and heterocyclization reactions based on 1,4-dihydropyridines: 92KGS781.

Spiro[piperidine-4, *n'*-hetero(carbo)cycles]: 91UK2633.

Synthesis of 1,4-dihydropyridines in cyclocondensation reactions: 92KGS435.

Synthesis of pyridines using Vilsmeier and inverse Vilsmeier methods: 93H(35)539.

Vinylacetylenic piperidine derivatives and polymers: 91MI2.

f. *Biologically Active Pyridines and Hydropyridines.* 1,4-Dihydropyridines, effects of chirality and conformation on activity of Ca antagonists and agonists: 91AG(E)1559.

Drugs, derivatives of  $\gamma$ -substituted piperidines: 91KFZ(7)61.

Neuropharmacologic activity of piperidine derivatives: 91KFZ(7)20.

g. *Pyridines Annulated with Carbocycles.* Advances in the synthesis of quinolines with antibacterial properties: 92H(34)2143.

Arenechromiumtricarboxyl-stabilized benzyl carbocations in asymmetric synthesis of tetrahydroisoquinolines: 93SL323.

Chemistry of 3-nitroquinolines and their derivatives: 92FKZ(4)43.

3(2*H*)-Isoquinolinones and their saturated derivatives: 91AHC(52)155.

Molecular design and a novel synthesis of quinolines: 93KGS962.

1,10-Phenanthroline-based complexes as artificial enzymes: 93CRV2295.

Pyridine ring closure on Combes synthesis of quinolines: 92KGS1011.

Stereocontrolled synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinoline derivatives using chromium tricarboxyl: 90JOM(400)223.

Synthesis and properties of secondary enamines of the 1,2,3,4-tetrahydroisoquinolylidenecarboxylic acid series: 90MI7.

Synthesis of fluoroquinolonecarboxylic acids: 91MI43.

Synthesis of molecular cavities with fused pyridine fragments: 92SL13.

Synthesis of quinolines and related systems using Vilsmeier and inverse Vilsmeier methods: 93H(35)539.

h. *Pyridines Annulated with Heterocycles.* Approaches to the synthesis of antitumor pyridocarbazole alkaloids: 91SL289.

Preparation of pyridoindoles, azaindoles, and indolopyridoimidazoles using Fischer indolization: 93H(36)157.

Pyrroloquinolines: 91OPP67.

Structure, synthesis, and biochemistry of marine pyridoacridine alkaloids: 93CRV1825.

Substituted 10*H*-pyrido[1,2-*a*]indolium salts, synthesis: 91MI24.

Synthesis of 7*H*-pyrido[2,3,4-*kl*]acridines related to marine alkaloids: 92H(34)2385.

Synthesis of pyrido[3,2,1-*kl*]-1,4-phenothiazine, quino[8,1-*bc*]-1,4-benzothiazepine, and their derivatives: 92JHC675.

Thiazolo- and oxazolo[3,2-*a*]pyridinium systems, synthesis: 91KGS1155.

## 2. One Oxygen Atom

a. *Pyrylium Compounds*. Dimerization of 2-benzopyrylium salts: 93 KGS3.

b. *Pyrans and Hydropyrans*. Arenechromiumtricarbonyl-stabilized benzyl carbocations in the asymmetric synthesis of 2-aryltetrahydropyrans: 93SL323.

Dehydracetic acid, triacetic acid lacton, and related pyrones: 92AHC(53)1.

Diels–Alder cycloaddition of 2-pyrones: 92T9171.

Electroconductive charge-transfer complexes and ion-radical salts from 4,4'-bipyranilidenes and bi(chalcogenopyranilidenes): 93MI17.

Prelog–Djerassi lactonoacid, stereoselective synthesis: 91S245.

Simple tetrahydropyran derivatives in syntheses of natural products: 91MI60.

Stereocontrolled transformations of diastereomeric pyranosides: 91SL529.

Stereoelectronic effects in unsaturated monosacharides: 91H(32)795.

Substituted pyrans: 92MI7.

Synthesis of  $\delta$ -lactones from unsaturated alcohols and CO catalyzed by Pd complexes: 91YGK909.

Synthesis of optically pure  $\delta$ -lactones using asymmetric reduction by baker's yeast: 91YGK647.

Synthesis of  $\text{CF}_3$ -substituted tetrahydropyrans: 91YGK624.

Terpene  $\delta$ -lactone forskolin, syntheses and physiological activity: 91MI33.

Tetrahydropyran derivatives as chiral auxiliaries: 92PAC1925.

c. *Annulated Pyrans and Pyrylium Salts*. Anthocyanines as flower pigments, dependence of color on their structure and molecular packing: 91AG(E)17.

Chemistry of rose pigments: 91AG(E)654.

Flavonoids as potential antiallergic compounds: 91KFZ(2)4.

Flavonoids from *Scutellaria* L. genus: 93MI24.

Heterocycles annulated at the 3,4-bond of 1-benzopyrans: 90JIC5.

HPLC of coumarin derivatives: 93KPS171.

Mass spectrometry of prenylated flavonoids: 92H(33)405.

Photochemical reactions of furocoumarin and related compounds: 91 YGK809.

Photochemistry of coumarines: 92UK1243.

Photochemistry of xanthene dyes: 93MI12.

Structure and functions of oligomeric flavanoids: 92T1743.

2-Styrylchromones, bioactivity, synthesis, and reactivity: 93H(36)2601.

Substituted benzopyrans: 92MI7.

Synthesis of biologically active  $\alpha$ -tocopherol esters: 91MI29.

Syntheses of tricyclic derivatives of chromanone related to cardiotonic forskoline: 92T963.

Syntheses, reactions, and physical properties of benzopyrylium salts: 90AHC(50)157.

Synthesis of pyranopyrazoles: 91G185.

### 3. *One Sulfur Atom*

Advances in the chemistry of thiopyranes, selenopyranes, and telluopyranes: 93AHC(59)179.

Asymmetric synthesis of 5,6-dihydro-7*H*-thieno[2,3-*b*]thiopyran 4,4-dioxide derivatives as carbonic anhydrase inhibitors: 92JHC627.

Chemistry of stabilized 2*H*-thiopyranes: 91PS(59)17.

Formation of  $\Delta^3$ -dihydrothiopyran-*S*-oxides via cycloaddition of  $\alpha$ -oxosulfines with dienes: 89P(43)S1.

Properties, syntheses, and reactions of 2*H*- and 4*H*-thiopyrans: 93MI19.

2,4,6,8-Tetrathiaadamantanes: 91UK736.

## C. TWO HETEROATOMS

### 1. *Two Nitrogen Atoms*

a. *1,2-Heterocycles: Pyridazines and Hydropyridazines.* Annulation of 5-, 6- and 7-membered rings to the pyridazine cycle: 93H(35)519.

1,3-Dipolar cycloaddition reactions of azolo- and azinopyridazines with diazoalkanes: 91T2925.

Progress in pyridazine chemistry: 92BSB579.

b. *1,3-Heterocycles: Monocyclic Pyrimidines and Hydropyrimidines (Except Pyrimidine Nucleoside Bases and Nucleosides).* Biginelli synthesis of dihydropyrimidines: 93T6937.

Ligand exchange in sulfuranes containing 2-pyrimidinyl substituents: 91PS(59)79.

Reactions of 4(6)-chloro-5-nitropyrimidines with nucleophilic agents: 93KFZ(4)26.

c. *Annulated Pyrimidines (Except Purines, Pteridines, and Flavins).* Fused pyrimidines inhibiting enzymes active in the metabolism of folic acid as new antitumor substances: 91KFZ(9)20.

Miscellaneous fused pyrimidines, general monograph: 92CH(24,4)1.

Synthesis and biological activity of tricyclic systems containing quinazoline annulated at its pyrimidine moiety by an other heterocycle: 91AHC(52)1.

Synthesis and properties of imidazo[1,2-*c*]pyrimidines: 91WCH177.

Synthesis and properties of pyrimido[1,2-*c*]pyrimidines: 91WCH707.

Synthesis of thiazolo[3,2-*a*]pyrimidines: 91MI49.

1,2,4-Triazolo[1,5-*a*]pyrimidines: 93AHC(57)81.

d. *Pyrimidine Nucleoside Bases, Purines, Nucleotides, Nucleosides, and Nucleic Acids.* Chemically modified oligonucleotides as tracers and inhibitors: 91AG(E)613.

Chemistry of anti-HIV 2,3-dideoxynucleotides and their analogs: 92CRV1745.

Chemistry of damage and repair of thymine and derivatives of thymidine: 93H(35)461.

2,3-Dideoxyfuranoses in convergent syntheses of 2,3-dideoxynucleosides: 92S1.

Electron impact mass spectrometry of cytosine and isocytosine derivatives: 93WCH51.

1-(2-Hydroxyethoxy)methyl-6-phenylthiothymine as an agent active against HIV-1: 91YGK1142.

Interaction of metal ions with nucleotides: 93CSR225.

Kinetic isotope effects in enzymatic reactions of purines: 92UK1822.

Methods for the study of defects and regeneration of DNA: 91CLY377.

Modified oligonucleotides, synthesis by phosphoramidite method and application: 93T6123.

Natural nucleosides, mass-spectrometric structural characteristics: 91ACR81.

Oligonucleotide functionalization through phosphorus amidite derivatives: 93T1925.

Oxidative modification of nucleic acids: 93UK70.

Peroxyl radicals of nucleic acids and of their components: 90WCH235.

Photochemistry of nucleic acids: 90MI26.

Preparation and modification of nucleic acids using condensation in aqueous solution: 92YGK24.

Preparation of nucleoside phosphorothioates, phosphorodithioates, and related compounds: 91MI50.

Purine and pyrimidine bases as ligands in enzymes, estimation of protein-ligand binding by enzyme inhibitors: 91ACR209.

Pyrimidine nucleosides and their analogs as uridine phosphorylase inhibitors and potential chemotherapeutic agents: 91CLY171.

Radical reactions of nucleic acids: 90WCH217.

Reactions of the lactam fragment of nucleic bases: 93MI29.

RNA pseudoknots: 91ACR152

Role of heteroaromaticity in quaternary DNA structures: 92H(34)1631.

Solid-phase NMR investigation of the structure and dynamics of DNA: 91CRV1545.

Structure, function, and stability of ribonuclease T1: 91AG(E)343.

Substituted xanthines, synthesis of: 91KGS3.

N<sub>5</sub>-Substituted nucleoside analogs: 92SL179.

Synthesis and biological activity of fused purines: 92KFZ(3)75.

Synthesis of chiral carbocyclic nucleotides, nucleoside analogs with fragments of 5-membered carbocyclic polyols instead of the glycosyl group: 92T571.

Synthesis of cytokinines of the purine series: 91MI30.

Synthesis of nucleosides using condensation reactions: 92YGK535.

Synthesis of oligonucleotide analogs with modified side chains: 93SL621.

Synthesis of specific ribonucleotides by the phosphoramidite method: 93T10441.

Synthesis, transformations, and biological properties of nucleosides modified by sulfur and seleno sugars: 93T9877.

e. *Pteridines*. Chemistry of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid as an antitumor factor: 93H(35)1527.

Pteridines, general review: 92JHC583.

f. *Flavins*. Oxidation using flavine models: 92YGK899.

g. *1,4-Heterocycles: Pyrazines and Hydropyrazines*. Piperazine-1,5-diones and related lactim ethers: 93AHC(57)187.

h. *Annulated Pyrazines*. Pyrrolo[1,2-*a*]pyrazines, synthesis and properties: 91KGS1299.

Synthesis and thermal and photochemical reactions of quinoxaline 1,4-dioxides and phenazine 9,10-dioxides: 93H(35)1503.

## 2. One Nitrogen and One Oxygen Atom

Chemistry of compounds with a morpholine ring: 91MI13.

Chemistry of 1,3-oxazin-4- and -6-ones: 92YGK887.

Synthesis and photochromic properties of spirooxazines: 91YGK392.

### 3. *One Nitrogen and One Sulfur Atom*

Functionalization of the dihydrothiazine ring in cephem sulfones: 93H(36)1747.

Synthesis of pyrido[3,2,1-*k*]-1,4-phenothiazine and its derivatives: 92JHC675.

1,3-Thiazines: 90AHC(50)85.

### 4. *Two Oxygen Atoms*

Chemistry of 1,3-dioxines: 91OPP593.

1,3-Dioxane-4,6-diones in organic synthesis: 91KGS579.

Dioxines and ecology: 93MI6.

Formation of 1,2-diox-4-enes by photooxidation of 1,3-dienes: 91T1343.

Meldrum's acid in organic synthesis: 91H(32)529.

Phase-transfer catalysis in the chemistry of 1,3-dioxanes: 92MI8.

Polychlorinated dibenzo-*p*-dioxines: 91CLY158.

### 5. *One Oxygen and One Sulfur Atom*

Chiral 1,3-oxathianes in asymmetric syntheses: 91PAC1591.

### 6. *Two Sulfur Atoms*

Conformation analysis of 1,3-dithianes and of their O- and Se-analogs with organophosphorus substituents: 93PS(74)311.

## D. THREE-HETEROATOMS

### 1. *Three Nitrogen Atoms*

Advances in the chemistry of *As*-triazinium salts: 92H(33)931.

Synthesis and reactivity of fused *As*-triazines with a bridgehead nitrogen atom: 92BSB5976.

Synthesis of 1,3,5-triazine derivatives from iminoesters of carboxylic acids: 92KGS1587.

2-(2,3,5-Tri-*O*-acetyl-*O*-ribofuranosyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (azaribine) in chemotherapy for psoriasis: 91CCC945.

1,2,4-Triazines fused with 3-, 4- or 5-membered heterocycles: 93AHC(59)39.

X-ray study of *N*-arylsulfonyl-*N'*-(1,3,5-triazyn-2-yl)ureas: 93KGS969.



## 2. *Two Nitrogen Atoms and One Sulfur Atom*

Functional derivatives of 1,3,4-thiadiazines and of fused systems on their base, synthesis and properties: 91KGS1443.

1,2,3-, 1,2,4-, 1,2,5-, And 1,2,6-thiadiazines: 90AHC(50)255.

1,3,4-Thiadiazines, synthesis and reactivity: 91KGS435.

## E. FOUR HETEROATOMS

### 1. *Four Nitrogen Atoms*

Synthesis and ring-chain tautomerism of hexahydro-1,2,4,5-tetrazine-3-thiones: 93KGS991.

Triphenylverdazyl radicals as indicators in studies of kinetics and mechanisms of monomolecular heterolysis of organic compounds: 91UK2089.

### 2. *Three Nitrogen Atoms and One Sulfur Atom*

Syntheses, reactions, and structure of 1,2,4,6-thiatriazines: 92MI21.

### 3. *Other Six-Membered Systems with Four Heteroatoms*

1,2,3,5-Oxathiadiazine-2,2-dioxides, 1,4,3,5-oxathiadiazine-4,4-dioxides, and 1,2,4,5-oxadithiazine-2,2,4,4-tetraoxides formed from cyano compounds and SO<sub>3</sub>: 93MI22.

## VII. Rings with More Than Six Members

### A. SEVEN-MEMBERED RINGS

#### 1. *General*

1,7-Electrocyclic reactions of  $\alpha, \beta, \gamma, \delta$ -unsaturated 1,3-dipoles as a route to 7-membered heterocycles: 91S181.

Synthesis of 7-membered heterocycles using ring expansion: 93T10749.

#### 2. *One Heteroatom*

Azepines: 91T9131.

Didehydroazepines as intermediates in the photolysis of aromatic azides: 92UK910.

### 3. *Two Heteroatoms*

a. *Two Nitrogen Atoms.* Arenechromiumtricarbonyl-stabilized benzyl carbocations in the asymmetric synthesis of tetrahydrobenzazepines: 93SL323.

1,5-Benzodiazepines annulated with 3-, 4- and 5-membered rings: 93H(36)601.

1,5-Benzodiazepines annulated with 6-membered rings: 93H(36)865.

Bicyclic 1,2-diazepines, general monograph: 91CH(50)1.

2,3-Dihydro, 1,4-diazepines and 2,3-dihydro, 1,4-diazepinium salts: 93AHC(56)1.

b. *One Nitrogen and One Sulfur Atom.* Synthesis of quino[8,1-*bc*]-1,4-benzothiazepine and its derivatives: 92JHC675.

c. *Two Sulfur Atoms.* Asymmetric reactions of chiral derivatives of dinaphtho[2,1-*d*;1',2'-*f*]-1,3-dithiepine: 93PS(74)195.

### 4. *Five Heteroatoms*

Trithiadiazepines: 92JHC639.

## B. MEDIUM RINGS

### 1. *General Problems*

Synthesis of 7- to 11-membered heterocycles using ring expansion: 93T10749.

### 2. *One Heteroatom*

Azocines and azonines: 91T9131.

### 3. *Two and More Heteroatoms*

Asymmetric reactions of chiral derivatives of dinaphtho[2,1-*e*;1'2'-*g*]-1,4-dithiocine, dinaphtho[2,1-*f*;1',2'-*h*]-1,5-dithiocine, dibenzo-[2,1-*e*;1',2'-*g*]-1,4-dithiocine, and 6*H*,12*H*-dibenzo[*b,f*]-1,5-dithiocine: 93PS(74)195.

1,2-Diazocines, 1,3-diazocines, triazocines, and tetrazocines: 90AHC(50)1.

1,5,2,6,3,7-Dioxadithiadiazocine-2,2,6,6-tetraoxides formed from cyano compounds and SO<sub>3</sub>: 93MI22.

Formation of dicationic salts based on 1,5-dithia- and 1,5-diselenacyclooctanes and the respective benzo- and naphtho-annulated systems: 93PS(74)261.

## C. LARGE RINGS

### 1. *General Problems*

a. *Structure, Stereochemistry, Reactivity, Design.* Macroheterocycles as host molecules and mechanisms of molecular recognition: 91AG(E)1417.

Macroheterocycles in analytical chemistry: 93MI3.

Macroheterocycles in host-guest reactions: 92AG(E)528.

Shapes and conformations of macroheterocycles: 92AG(E)1124.

b. *Synthesis.* Design and synthesis of O-macroheterocycles as artificial ionic channels: 93SL449.

c. *Applications.* N- and S-Macroheterocycles and their complexes as low-molecular enzyme models: 91UK2497.

### 2. *Crown Ethers and Related Compounds*

Aza-crown macrocycles, general monograph: 93CH(51)1.

Complex-forming and membrane-active properties of crown ethers: 91MI4.

Conformational analysis of free and complexed crown ethers in solution: 91JPR817.

Coordination compounds of metals with crown ligands: 91MI5.

Crown ethers as components of selective mobile and stationary phases in chromatography: 93ZAK582.

Crown ethers and cryptands, a monograph: 91MI37.

Crown ethers and their aza analogs as ligands: 92UK415.

Crown ethers, azacrown ethers, and related compounds, thermodynamic and kinetic data on their interaction with cations and anions: 91CRV1721.

Crown ethers bearing side chains: 92CSR139.

Crown ethers in the separation of rare-earth elements: 92CLY77.

Enantioselective formation of the C-C bond with participation of thiacycrown metal complexes as enzyme models: 92PAC413.

Lithium complexes of crown ethers: 91CRV137.

Macrocyclic polyethers and related compounds: 92CRV543.

Methods for the synthesis of diazacoronands and cryptands: 90WCH193.

Nitro- and aminobenzocrowns, preparation and practical applications: 90MI9.

Radiation chemistry of crown ethers: 92UK883.

Reactions of crown ethers catalyzed by metal ions: 93CSR221.

Syntheses and use of functionally substituted crown ethers: 91MI44.

Syntheses of aza-crowns and cryptands: 93SL611.

Thermodynamics of complex-formation of alkali metal salts with crown ethers: 91MI12.

### 3. *Macrocyclic Lactones*

Highly stereocontrolled synthesis of 2,6-dideoxy sugars and its use in the synthesis of macrolide antibiotics: 92YGK303.

Nonpolyenic antifungal macrolide antibiotics: 91MI27.

Total synthesis of aglycone of venturicidines A and B: 90YZ789; 91YGK657.

Total synthesis of macrolide and ionophore antibiotics containing fragments of tetronic acid: 92YZ358.

### 4. *Miscellaneous Macroheterocycles*

a. *Macrocyclic Amides, Amines, and Imines.* Advances in the synthesis of macrolactams: 91MI23.

Macrocyclic polyamines with reasonable functions: 92T6175.

b. *Other Systems.* Autoassembly of catenanes and rotaxanes containing heteroatoms and heterocyclic fragments: 91SL445.

Molecular recognition of immunophilins (macrocyclic O- and N-heterocycles with immunodepressant properties) and of complexes with immunophilin ligands: 92T2545.

2,3-Sigmatropic Wittig rearrangement of macrocyclic allyl propargyl ethers to carbocycles: 91TA1.

## VIII. Heterocycles Containing Unusual Heteroatoms

### A. GROUP V ELEMENT HETEROCYCLES

#### 1. *Phosphorus Heterocycles*

a. *Chemistry of Individual Classes of P-Heterocycles.* Bicyclophosphorylated carbohydrates: 93ZOB481.

Complexes of metallaphosphaheterocycles: 92PS(64)77.

Cyclic aminophosphoranes, synthesis and transformations: 91UKZ1291.

Eight-membered P-heterocycles: 92PS(68)155.

Heterocycles of low-coordinated phosphorus: 92BSB609.

B,P-Heterocycles: 92UK616.

P,O-Heterocycles related to salicylic acid: 92UK1839.

Saturated 4-membered P,O-, P,S-, and P,N-heterocycles: 92H(33)369.

b. *Structure and Stereochemistry.* Correlations of  $^{31}\text{P}$  chemical shifts in cyclic oxyphosphoranes: 93PS(80)1.

c. *Reactivity.* P-Heterocycles as intermediates in the oxidative phosphorylation of organic compounds with phosphorus and phosphides in the presence of metal complexes: 93UK928.

1,2-Oxaphosphetanes as Wittig reaction intermediates: 92CLY662.

Preparation and ring-opening polymerization of N,Si, P,Si-, and S,Si-heterocycles: 92YGK35.

Substitution reactions in cyclophosphazenes, regio- and stereochemical control: 91CRV119.

d. *Synthesis.* Five-membered P,O-heterocycles as phosphorylating agents: 93S1.

Formation of P-, P,O-, and P,N-heterocycles using Staudinger reaction: 92T1353.

Heterocyclization of ketoalkoxyl derivatives of acids of tricoordinated phosphorus: 91ZOB10.

Iminophosphanes in the synthesis of N,P- and N,P,X-heterocycles: 91AG(E)217.

Methods for the synthesis of nitro-substituted phospholene-1,1-dioxides: 93ZOB241.

Monocyclic and polycyclic phosphanes: 93CRV1623.

Phosphatranes: 93ACR483.

Synthesis of P-heterocycles from phosphalkynes: 92BSB359.

Synthesis and reactivity of cyclic phosphazenes: 91OPP1.

Synthesis, structure, and reactivity of cyclic diphosphenes: 92CRV1839.

Synthesis of 6- and 7-membered P-heterocycles using ring expansion: 93S931.

Three- and four-membered N,P-heterocycles as precursors of iminophosphanes: 91AG(E)217.

Transition-metal complexes of cyclic di-, tri-, and polyphosphanes and phosphines: 91CRV575.

Tungstaphosphirenes: 1,2-dihydrophosphetes, dihydrodiphosphetes, and dihydrophosphepines: 93PS(77)69.

## 2. *Arsenic and Antimony Heterocycles*

As-Heterocycles, formation and reactions: 91UK317.

Sb-Heterocycles: 93MI20.

Synthesis, structure, and reactivity of As- and Sb-analogs of cyclic diphosphenes: 92CRV1839.

## B. BORON HETEROCYCLES

### 1. *Chemistry of Individual Classes of B-Heterocycles*

Benzannulated cycloboranes: 91PAC383.

Boratrane: 93ACR483.

Carboranes and related compounds: 92CRV177, 92CRV209, 92CRV225.

Carboranylcarbenes: 93IZV637.

Carboranyl derivatives of nontransition metals: 91PAC835.

Chemistry of bis(9-borabicyclo[3.3.1]nonane): 91PAC387.

Chemistry of polyhedral boranes: 91PAC317.

Heterocarboranes of main groups: 91PAC375.

B,N-Heterocycles: 88MI; 91PAC345.

B,N,O-Heterocycles: 93KK5.

B,P-Heterocycles: 92UK616.

Three-membered B-heterocycles: 92AG(E)1329.

### 2. *Structure and Stereochemistry*

Character of bonding in metallacarboranes: 91NJC831.

<sup>11</sup>B NMR spectroscopy of B-heterocycles: 92CRV325.

Three-dimensional aromaticity in deltaedric boranes and carboranes: 93IZV1353.

Vibrational spectroscopy of B-heterocycles: 92CRV279.

### 3. *Reactivity*

Asymmetric reduction with chiral B-heterocycles based on  $\alpha$ -pinene: 92ACR16.

### 4. *Synthesis*

Carboranyl derivatives of mercury and thallium as synthons for boron-substituted carboranes: 91PAC357.

Photorearrangement of  $\alpha,\beta$ -unsaturated organoboranes in synthesis of borirenes: 91PAC365.

Synthesis of B,N- and B,N,O-heterocycles: 91PAC396.

### 5. *Applications*

Biological uses of boron clusters: 91PAC327.

Boranylated DNA as potential neutron-capture agents: 91PAC415.

Chiral oxazaborolidines as chemzymes: 92MI40.

Cyclic boronates in asymmetric synthesis: 91PAC339.

B-Heterocycles as agents of hydroboration: 91CRV1179.

B-Heterocycles as ligands in organometallic synthesis: 92CRV251.

B-Heterocycles in the synthesis of organometallic polymers: 91UK1553.

Molecular design and synthesis of boron carriers for neutron-capture tumor therapy: 91PAC423.

Oxaborolidine, 9-borabicyclo[3.3.1]nonane, and 2,5-dimethylborolane derivatives as catalysts for the asymmetric reduction of ketones: 92S605.

Precursors of carboranyl nucleic acids used in neutron-capture tumor therapy: 91PAC411.

Small carboranes as building blocks in directed organometallic synthesis: 91PAC369.

## C. SILICON, GERMANIUM, TIN, AND LEAD HETEROCYCLES

### 1. *Chemistry of Individual Classes of Heterocycles*

Furyl- and thienyl-substituted silatranes and germatranes: 92KGS725.

Spirocyclic compounds of siloxane series: 93UK208.

### 2. *Structure and Stereochemistry*

Strained Si-, Ge-, and Sn-heterocycles: 91AG(E)902.

### 3. *Reactivity*

Addition of nitrogen reagents to unsaturated Si-heterocycles: 92MI37.

Si-Heterocycles in photochemical reactions: 91CLY337.

Si- and Ge-Heterocycles, vacuum pyrolysis of: 91PAC231.

Reactivity of Si-heterocycles with penta- and hexa-coordinated Si atoms: 93CRV1371.

Silacyclopentane derivatives in Peterson olefination: 91SL764.

2,2,6,6-Tetramethyl-2,6-disilapiperidine in the Gabriel synthesis of primary amines: 91ACR285.

### 4. *Synthesis*

Direct synthesis of Ge-heterocycles: 93MI31.

Formation of Ge- and Sn-heterocycles in reactions of germynes and stannylenes: 91CRV311.

Ge,S- and Si,S-Heterocycles, formation in reactions of sulfur with carbene analogs: 91PS(58)179.

Silatranes, stannatranes, and germatranes: 93ACR483.

## D. SELENIUM AND TELLURIUM HETEROCYCLES

### 1. *General Sources and Topics*

Dications, derivatives of Se- and Te-heterocycles with two heteroatoms: 91YGK636.

Se- and Te-Heterocycles, radical reactions and formation on radical reactions: 93UK1173.

### 2. *Chemistry of Individual Classes of Heterocycles*

Advances in chemistry of selenopyranes and telluropyrans: 93AHC(59)179.

1,3- and 1,2-Ditellurols, synthesis, reactions, and structures: 91KGS291.

Tellurium-containing heterocycles with two heteroatoms: 93AHC(58)47.

### 3. *Reactivity*

1,3,4-Selenadiazoles, reaction with sulfur: 91PS(58)179.

### 4. *Synthesis*

Formation of dicationic salts based on 1,5-diselenacyclooctane and respective benzo- and naphtho-annulated systems: 93PS(74)261.

Formation of selenophene derivatives on chalcogenation in multiphase superbase systems: 92MI24.

Formation of Te-heterocycles from vinyl tellurides: 91MI51.

### 5. *Practical Applications*

Conducting charge-transfer salts based on Se and Te analogs of bis-ethylthiotetrathiafulvalene: 91CSR355.

## E. OTHER UNUSUAL HETEROCYCLES

Alumatranes and titanatranes: 93ACR483.

Bicyclic Zr, Hf, and lanthanide chelates with tridentate N,P-containing ligands: 91PAC845.



- Character of bonding in metallocarboranes: 91NJC831.  
 Chemistry of alkylaromatic 5-membered palladacycles: 93G1.  
 Chemistry of metallabenzenes: 91ACR271.  
 Chiral 7-membered cyclic titanates as reagents in asymmetric synthesis: 92PAC1897.  
 Chiral Ni(II)-, Cu(II)-, and Cu(I)-chelates as reagents, catalysts, and receptors in asymmetric synthesis and chiral recognition of amino acids: 92PAC1917.  
 Exoalkylidene-1-elementacyclobutenyl ligands: 92SL681.  
 Al- and Ga-Heterocycles: 93AG(E)1386.  
 Inorganic N,S-heterocycles: 92JHC639.  
 Metal chelates in the synthesis of radioisotope labeled monoclonal antibodies: 91PAC427.  
 Metallocarboranes: 93CRV1081.  
 Metallocycles based on Te and other radioactive elements in nuclear medicine: 93CRV1137.  
 Metallocycles, formation from carbene complexes of transition metals: 91UK169.  
 Metallocycles in the gas phase: 91CRV1121.  
 Metalladiaziridines and other N-containing metallocycles: 93CRV995.  
 Metallomezogenes, linear liquid crystals including metallocycles: 93CRV661.  
 Metal-stabilized cage chalcogenonitrides (inorganic N,S,Se,*M*-, N,S,Te,*M*, N,S,*M*, and N,Se,*M*-heterocycles with *M* = Ir, Rt): 92CSR245.  
 Se- and Te-containing inorganic metallocycles: 93CRV1037.  
 Synthesis of metallocyclobutenes via  $\eta^3$ -vinylcarbene complexes: 91NJC769.  
 Titanium metallocycles as intermediates in the synthesis of acyclic and heterocyclic compounds: 92SL13.  
 Vanadium heterocycles: 91AG(E)148.

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